IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

UNEP

Environmental Health Criteria 210

Principles for the Assessment of Risks to Human Health from Exposure to Chemicals

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among UNEP, ILO, FAO, WHO, UNIDO, UNITAR and OECD

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This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organisation, or the World Health Organization.

Environmental Health Criteria 210

PRINCIPLES FOR THE ASSESSMENT OF RISKS TO HUMAN HEALTH FROM EXPOSURE TO CHEMICALS

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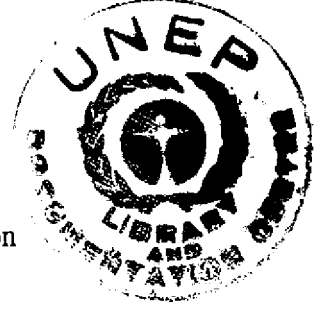

World Health Organization
Geneva, 1999

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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PRINCIPLES FOR THE ASSESSMENT OF RISKS TO HUMAN HEALTH FROM EXPOSURE TO CHEMICALS

NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (telephone no. + 41 22 – 9799111, fax no. + 41 22 – 7973460, E-mail irptc@unep.ch).

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Environmental Health Criteria

P R E A M B L E

Objectives

In 1973 the WHO Environmental Health Criteria Programme was initiated with the following objectives:

(I) to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits;

(ii) to identify new or potential pollutants;

(iii) to identify gaps in knowledge concerning the health effects of pollutants;

(iv) to promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results.

The first Environmental Health Criteria (EHC) monograph, on mercury, was published in 1976 and since that time an ever-increasing number of assessments of chemicals and of physical effects have been produced. In addition, many EHC monographs have been devoted to evaluating toxicological methodology, e.g., for genetic, neurotoxic, teratogenic and nephrotoxic effects. Other publications have been concerned with epidemiological guidelines, evaluation of short-term tests for carcinogens, biomarkers, effects on the elderly and so forth.

Since its inauguration the EHC Programme has widened its scope, and the importance of environmental effects, in addition to health effects, has been increasingly emphasized in the total evaluation of chemicals.

The original impetus for the Programme came from World Health Assembly resolutions and the recommendations of the 1972 UN Conference on the Human Environment. Subsequently the work became an integral part of the International Programme on Chemical Safety (IPCS), a cooperative programme of UNEP, ILO and WHO. In this manner, with the strong support of the new partners, the importance of occupational health and environmental effects was fully

recognized. The EHC monographs have become widely established, used and recognized throughout the world.

The recommendations of the 1992 UN Conference on Environment and Development and the subsequent establishment of the Intergovernmental Forum on Chemical Safety with the priorities for action in the six programme areas of Chapter 19, Agenda 21, all lend further weight to the need for EHC assessments of the risks of chemicals.

Scope

The criteria monographs are intended to provide critical reviews on the effect on human health and the environment of chemicals and of combinations of chemicals and physical and biological agents. As such, they include and review studies that are of direct relevance for the evaluation. However, they do not describe *every* study carried out. Worldwide data are used and are quoted from original studies, not from abstracts or reviews. Both published and unpublished reports are considered and it is incumbent on the authors to assess all the articles cited in the references. Preference is always given to published data. Unpublished data are only used when relevant published data are absent or when they are pivotal to the risk assessment. A detailed policy statement is available that describes the procedures used for unpublished proprietary data so that this information can be used in the evaluation without compromising its confidential nature (WHO (1990) Revised Guidelines for the Preparation of Environmental Health Criteria Monographs. PCS/90.69, Geneva, World Health Organization).

In the evaluation of human health risks, sound human data, whenever available, are preferred to animal data. Animal and *in vitro* studies provide support and are used mainly to supply evidence missing from human studies. It is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration.

The EHC monographs are intended to assist national and international authorities in making risk assessments and subsequent risk management decisions. They represent a thorough evaluation of risks and are not, in any sense, recommendations for regulation or

standard setting. These latter are the exclusive purview of national and regional governments.

Content

The layout of EHC monographs for chemicals is outlined below.

- Summary — a review of the salient facts and the risk evaluation of the chemical
- Identity — physical and chemical properties, analytical methods
- Sources of exposure
- Environmental transport, distribution and transformation
- Environmental levels and human exposure
- Kinetics and metabolism in laboratory animals and humans
- Effects on laboratory mammals and *in vitro* test systems
- Effects on humans
- Effects on other organisms in the laboratory and field
- Evaluation of human health risks and effects on the environment
- Conclusions and recommendations for protection of human health and the environment
- Further research
- Previous evaluations by international bodies, e.g., IARC, JECFA, JMPR

Selection of chemicals

Since the inception of the EHC Programme, the IPCS has organized meetings of scientists to establish lists of priority chemicals for subsequent evaluation. Such meetings have been held in: Ispra, Italy, 1980; Oxford, United Kingdom, 1984; Berlin, Germany, 1987; and North Carolina, USA, 1995. The selection of chemicals has been based on the following criteria: the existence of scientific evidence that the substance presents a hazard to human health and/or the environment; the possible use, persistence, accumulation or degradation of the substance shows that there may be significant human or environmental exposure; the size and nature of populations at risk (both human and other species) and risks for environment; international concern, i.e. the substance is of major interest to several countries; adequate data on the hazards are available.

If an EHC monograph is proposed for a chemical not on the priority list, the IPCS Secretariat consults with the Cooperating Organizations and all the Participating Institutions before embarking on the preparation of the monograph.

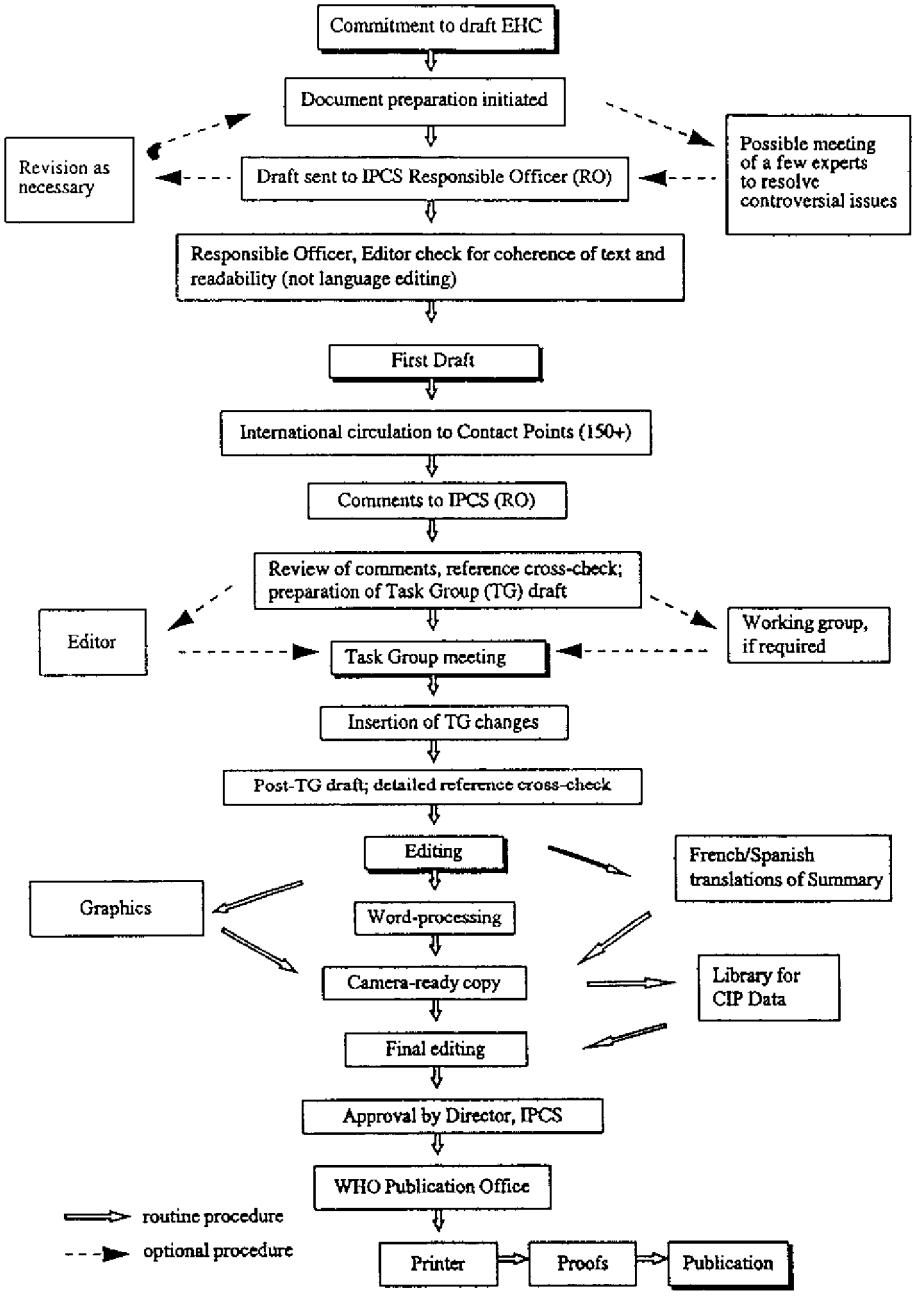
Procedures

The order of procedures that result in the publication of an EHC monograph is shown in the flow chart. A designated staff member of IPCS, responsible for the scientific quality of the document, serves as Responsible Officer (RO). The IPCS Editor is responsible for layout and language. The first draft, prepared by consultants or, more usually, staff from an IPCS Participating Institution, is based initially on data provided from the International Register of Potentially Toxic Chemicals, and reference data bases such as Medline and Toxline.

The draft document, when received by the RO, may require an initial review by a small panel of experts to determine its scientific quality and objectivity. Once the RO finds the document acceptable as a first draft, it is distributed, in its unedited form, to well over 150 EHC contact points throughout the world who are asked to comment on its completeness and accuracy and, where necessary, provide additional material. The contact points, usually designated by governments, may be Participating Institutions, IPCS Focal Points, or individual scientists known for their particular expertise. Generally some four months are allowed before the comments are considered by the RO and author(s). A second draft incorporating comments received and approved by the Director, IPCS, is then distributed to Task Group members, who carry out the peer review, at least six weeks before their meeting.

The Task Group members serve as individual scientists, not as representatives of any organization, government or industry. Their function is to evaluate the accuracy, significance and relevance of the information in the document and to assess the health and environmental risks from exposure to the chemical. A summary and recommendations for further research and improved safety aspects are also required. The composition of the Task Group is dictated by the range of expertise required for the subject of the meeting and by the need for a balanced geographical distribution.

EHC PREPARATION FLOW CHART



The three cooperating organizations of the IPCS recognize the important role played by nongovernmental organizations. Representatives from relevant national and international associations may be invited to join the Task Group as observers. While observers may provide a valuable contribution to the process, they can only speak at the invitation of the Chairperson. Observers do not participate in the final evaluation of the chemical; this is the sole responsibility of the Task Group members. When the Task Group considers it to be appropriate, it may meet *in camera*.

All individuals who as authors, consultants or advisers participate in the preparation of the EHC monograph must, in addition to serving in their personal capacity as scientists, inform the RO if at any time a conflict of interest, whether actual or potential, could be perceived in their work. They are required to sign a conflict of interest statement. Such a procedure ensures the transparency and probity of the process.

When the Task Group has completed its review and the RO is satisfied as to the scientific correctness and completeness of the document, it then goes for language editing, reference checking, and preparation of camera-ready copy. After approval by the Director, IPCS, the monograph is submitted to the WHO Office of Publications for printing. At this time a copy of the final draft is sent to the Chairperson and Rapporteur of the Task Group to check for any errors.

It is accepted that the following criteria should initiate the updating of an EHC monograph: new data are available that would substantially change the evaluation; there is public concern for health or environmental effects of the agent because of greater exposure; an appreciable time period has elapsed since the last evaluation.

All Participating Institutions are informed, through the EHC progress report, of the authors and institutions proposed for the drafting of the documents. A comprehensive file of all comments received on drafts of each EHC monograph is maintained and is available on request. The Chairpersons of Task Groups are briefed before each meeting on their role and responsibility in ensuring that these rules are followed.

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[a] Participated in Planning and Working Groups on Scientific Principles for the Assessment of Risks to Human Health from Exposure to Chemicals.

[b] Participated in the WHO Task Group Meeting on the initial draft of Principles for the Assessment of Risk from Exposure to Chemicals (British Industry Biological Research Association (BIBRA), Carshalton, Surrey, United Kingdom, March 1993).

[c] Participated in the WHO Task Group Meeting on the initial draft of General Principles and Methods for Chemical Safety (Human Health Protection) (National Institute of Public Health and Environmental Protection (RIVM), Bilthoven, the Netherlands, 22–25 March 1994).

[d] Participated in the WHO Finalizing Group Meetings on Principles for the Assessment of Risks to Human Health from Exposure to Chemicals (World Health Organization, Geneva, Switzerland, 2–5 September 1996 and 18–20 September 1997).

PRINCIPLES FOR THE ASSESSMENT OF RISKS TO HUMAN HEALTH FROM EXPOSURE TO CHEMICALS

This monograph is an amalgamation of two draft documents "Principles for the Assessment of Risk from Exposure to Chemicals" and "General Principles and Methods for Chemical Safety (Human Health Protection)".

Both documents were planned to cover different aspects of chemical safety and risk assessment; one dealing with the basic science for general readers, and the other providing more practical approaches to risk assessment of chemicals for risk assessors. However, they turned out to have a substantial amount of overlapping information and it was therefore decided to use both drafts as a basis for this new, comprehensive document. The more detailed draft on "General Principles and Methods for Chemical Safety (Human Health Protection)" will be published as a separate document for training purposes.

This Environmental Health Criteria monograph is aimed at furnishing a practical overview of chemical safety and at providing the framework of risk assessment for regulatory and research scientists, as well as risk managers. It is intended to complement existing Environmental Health Criteria that address methodologies for the assessment of risks from exposure to chemicals with a view towards different end-points or to susceptible population groups. It is not intended as a textbook on toxicology.

This monograph should not be considered as being of a prescriptive nature. The chapters on exposure assessment and risk characterization, in particular, provide rather some practical guidance.

Several planning, working and Task Group meetings took place to discuss and agree upon the structures and contents of both Environmental Health Criteria documents.

A WHO Task Group on "Principles for the Assessment of Risk from Exposure to Chemicals" met at the British Industrial Biological Research Association (BIBRA), Carshalton, Surrey, United Kingdom, in March 1993. Dr G.C. Becking, IPCS, welcomed the participants on behalf of the Director, IPCS, and the three IPCS cooperating

organizations (UNEP/ILO/WHO), and the Task Group reviewed the draft document.

The main contributors to the first draft on Principles for the Assessment of Risk from Exposure to Chemicals were Dr N. Aldridge, Robens Institute of Industrial and Environmental Health and Safety, United Kingdom, Dr H. Gibb, US Environmental Protection Agency, Dr J. Huff, National Institute of Environmental Health Sciences, USA, Dr L Stayner, National Institute for Occupational Safety and Health, USA.

A second WHO Task Group met to review the draft monograph on General Principles and Methods for Chemical Safety (Human Health Protection). This group met in at the National Institute of Public Health and Environmental Protection (RIVM), Bilthoven, the Netherlands, from 22 to 25 November 1995. Dr E. Smith, IPCS, welcomed the participants on behalf of the Director, IPCS, and the three IPCS cooperating organizations (UNEP/ILO/WHO), and the Task Group reviewed the draft document.

The main contributors to the draft on Principles for the Assessment of Risk from Exposure to Chemicals were Dr D.B. Clayson, Carp, Canada, Professor E. Dybing, National Institute of Public Health, Norway, Dr L. Fishbein, Fairfax, Virginia, USA, Dr A.G. Renwick, University of Southampton, United Kingdom, Professor R. Walker, University of Surrey, United Kingdom, and Professor J.A Sokal, Institute of Occupational Health and Environmental Medicine, Sosnowiec, Poland.

In addition to the Task Group meetings, meetings were held during 1996 and 1997 in Geneva to combine the two documents.

Dr E. Smith and Dr G. Becking, both members of the IPCS, were responsible for the preparation of the initial draft documents. Dr M. Younes (IPCS) was responsible for the overall scientific content of the final monograph and Dr P.G. Jenkins (IPCS) for the technical editing.

The efforts of all who helped in the preparation and finalization of the document are gratefully acknowledged.

ABBREVIATIONS

ADD	average daily dose
ADI	acceptable daily intake
EPI	exposure/potency index
GLP	good laboratory practice
IARC	International Agency for Research on Cancer
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
PBPK	physiologically based pharmacokinetic
SAR	structure–activity relationship
US EPA	US Environmental Protection Agency

1. SUMMARY

Control of risks from exposure to chemicals (chemical safety) requires first of all a scientific, ideally quantitative, assessment of potential effects at given exposure levels (risk assessment). Based upon the results of risk assessment, and taking into consideration other factors, a decision-making process aimed at eliminating or, if this is not possible, reducing to a minimum the risk to the chemical(s) under consideration (risk management), can be started.

Risk assessment is a conceptual framework that provides the mechanism for a structured review of information relevant to estimating health or environmental outcomes. In conducting risk assessments, the National Academy of Sciences risk assessment paradigm has proven to be a useful tool (US NAS, 1983). This paradigm divides the risk assessment process into four distinct steps: hazard identification, dose–response assessment, exposure assessment and risk characterization.

The purpose of hazard identification is to evaluate the weight of evidence for adverse effects in humans based on assessment of all available data on toxicity and mode of action. It is designed to address primarily two questions: (1) whether an agent may pose a health hazard to human beings, and (2) under what circumstances an identified hazard may be expressed. Hazard identification is based on analyses of a variety of data that may range from observations in humans to analysis of structure–activity relationships. The result of the hazard identification exercise is a scientific judgement as to whether the chemical evaluated can, under given exposure conditions, cause an adverse health effect in humans. Generally, toxicity is observed in one or more **target organ**(s). Often, multiple end-points are observed following exposure to a given chemical. The **critical effect**, which is usually the first significant adverse effect that occurs with increasing dose, is determined.

Dose–response assessment is the process of characterizing the relationship between the dose of an agent administered or received and the incidence of an adverse health effect. For most types of toxic effects (i.e. organ-specific, neurological/behavioural, immunological, non-genotoxic carcinogenesis, reproductive or developmental), it is generally considered that there is a dose or concentration below which

adverse effects will not occur (i.e. a threshold). For other types of toxic effects, it is assumed that there is some probability of harm at any level of exposure (i.e. that no threshold exists). At the present time, the latter assumption is generally applied primarily for mutagenesis and genotoxic carcinogenesis.

If a threshold has been assumed (e.g., for non-neoplastic effects and non-genotoxic carcinogens), traditionally, a level of exposure below which it is believed that there are no adverse effects, based on a no-observed-adverse-effect level (NOAEL) (approximation of the threshold) and uncertainty factors, has been estimated. Alternatively, the magnitude by which the no (lowest)-observed-adverse-effect level (N(L)OAEL) exceeds the estimated exposure (i.e. the "margin of safety") is considered in light of various sources of uncertainty. In the past, this approach has often been described as a "safety evaluation". Therefore, the dose that can be considered as a first approximation of the threshold, i.e. the NOAEL, is critical. Increasingly, however, the "benchmark dose", a model-derived estimate (or its lower confidence limit) of a particular incidence level (e.g., 5%) for the critical effect, is being proposed for use in quantitative assessment of the dose–response for such effects.

There is no clear consensus on appropriate methodology for the risk assessment of chemicals for which the critical effect may not have a threshold (i.e. genotoxic carcinogens and germ cell mutagens). Indeed, a number of approaches based largely on characterization of dose–response have been adopted for assessment in such cases. Therefore, the critical data points are those that define the slope of the dose–response relationship (rather than the NOAEL, which is the first approximation of a threshold).

The third step in the process of risk assessment is the **exposure assessment**, which has the aim of determining the nature and extent of contact with chemical substances experienced or anticipated under different conditions. Multiple approaches can be used to conduct exposure assessments. Generally, approaches include indirect and direct techniques, covering measurement of environmental concentrations and personal exposures, as well as biomarkers. Questionnaires and models are also often used. Exposure assessment requires the determination of the emissions, pathways and rates of movement of a substance and its transformation or degradation, in

order to estimate the concentrations to which human populations or environmental spheres (water, soil and air) may be exposed.

Depending on the purpose of an exposure assessment, the numerical output may be an estimate of either the intensity, rate, duration or frequency of contact exposure or dose (resulting amount that actually crosses the boundary). For risk assessments based on dose–response relationships, the output usually includes an estimate of dose. It is important to note that the internal dose, not the external exposure level, determines the toxicological outcome of a given exposure.

Risk characterization is the final step in risk assessment. It is designed to support risk managers by providing, in plain language, the essential scientific evidence and rationale about risk that they need for decision-making. In risk characterization, estimates of the risk to human health under relevant exposure scenarios are provided. Thus, a risk characterization is an evaluation and integration of the available scientific evidence used to estimate the nature, importance, and often the magnitude of human and/or environmental risk, including attendant uncertainty, that can reasonably be estimated to result from exposure to a particular environmental agent under specific circumstances.

The term "risk management" encompasses all of those activities required to reach decisions on whether an associated risk requires elimination or necessary reduction. Risk management strategies/or options can be broadly classified as regulatory, non-regulatory, economic, advisory or technological, which are not mutually exclusive. Thus legislative mandates (statutory guidance), political considerations, socioeconomic values, cost, technical feasibility, populations at risk, duration and magnitude of risk, risk comparison, and possible impact on trade between countries can generally be considered as a broad panoply of elements that can be factored into final policy or rule making. Key decision factors such as the size of the population, the resources, costs of meeting targets and the scientific quality of risk assessment and subsequent managerial decisions vary enormously from one decision context to another. It is also recognized that risk management is a complex multidisciplinary procedure which is seldom codified or uniform, is frequently unstructured, but which can respond to evolving input from a wide variety of sources.

Increasingly, risk perception and risk communication are recognized as important elements, which must also be considered for the broadest possible public acceptance of risk management decisions.

Chemicals have become an indispensable part of human life, sustaining activities and development, preventing and controlling many diseases, and increasing agricultural productivity. Despite their benefits, chemicals may, especially when misused, cause adverse effects on human health and environmental integrity. The widespread application of chemicals throughout the world increases the potential of adverse effects. The growth of chemical industries, both in developing as well as in developed countries, is predicted to continue to increase. In this context, it is recognized that the assessment and management of risks from exposure to chemicals are among the highest priorities in pursuing the principles of sustainable development.

2. INTRODUCTION

Despite the societal benefits that accrue from the use of chemicals, substantial potential hazards to health may be associated with exposure during the production, use or disposal of the approximately 100 000 unique chemicals or 4 million mixtures, formulations and blends already in commercial use or the several hundred new synthetic chemicals introduced each year (EC, 1990). This monograph outlines the nature of the data available and their use in the assessment of risk in a risk assessment/risk management framework. It is hoped that scientists, risk assessors and health risk managers will find this monograph helpful to decision-making in this area.

A number of national and international organizations and agencies have developed guidance on assessment of exposure and various health end-points (e.g., carcinogenicity, developmental toxicity, etc.). It is not the purpose of this monograph to endorse particular approaches but rather to acquaint the reader with relevant methodology and issues for consideration.

It is also hoped that the reader will find this monograph useful in the interpretation of risk assessments on specific chemicals. The reader is referred to such sources for chemical-specific hazard identification and, depending on the monograph, dose–response information. A list of assessments produced by various national and international agencies is included in ECETOC/UNEP (1996). These sources do not, of course, provide the exposure information necessary to characterize risk at the local level. Since exposure will vary considerably under different circumstances, responsible authorities are strongly encouraged to characterize risk on the basis of local measured or predicted exposure scenarios. It is hoped that the general approaches to exposure assessment described in this monograph will assist the reader in characterizing risk in specific situations.

In the chapters of this monograph, the following four distinct and essential components of the risk assessment paradigm are addressed:

(1) *hazard identification* – identification of the inherent capability of a substance to cause adverse effects;

(2) *assessment of dose–response relationships* involves characterization of the relationship between the dose of an agent administered or received and the incidence of an adverse effect;

(3) *exposure assessment* is the qualitative and/or quantitative assessment of the chemical nature, form and concentration of a chemical to which an identified population is exposed from all sources (air, water, soil and diet);

(4) *risk characterization* is the synthesis of critically evaluated information and data from exposure assessment, hazard identification and dose–response considerations into a summary that identifies clearly the strengths and weaknesses of the database, the criteria applied to evaluation and validation of all aspects of methodology, and the conclusions reached from the review of scientific information.

The logical consequence of the process of assessment of potential risk is the application of the information to the development of practical measures (risk management) for the protection of human health. Although not the principal focus of this monograph, the importance of clear understanding and communication of the nature and limitations of the scientific basis for risk assessment in risk management is addressed in the final chapter.

In Appendix 1 to this monograph, an example of a hazard identification scheme for carcinogenicity, developed by the International Agency for Research on Cancer (IARC), is presented. In Appendix 2, the currently available and draft guidelines of the Organisation for Economic Cooperation and Development (OECD) for testing of chemicals are presented. For sample exposure and risk characterizations, readers are referred to IPCS (1994).

3. HEALTH HAZARD IDENTIFICATION

3.1 Introduction

The purpose of hazard identification is to evaluate the weight of evidence for adverse effects in humans based on assessment of all available data on toxicity and mode of action. It is designed to address primarily two questions: (a) whether an agent may pose a health hazard to humans, and (b) under what circumstances an identified hazard may be expressed. Hazard identification is based on analyses of a variety of data that may range from observations in humans to analysis of structure–activity relationships.

In hazard identification, the weight of evidence is assessed on the basis of combined strength and coherence of inferences appropriately drawn from all of the available data. This entails rigorous examination of the quantity, quality and nature of the results of available toxicological and epidemiological studies and structure–activity analyses and information on mechanisms of toxicity. The latter is particularly important with respect to assessment of relevance to humans.

Several classification schemes provide a framework for assessment of the weight of evidence for various toxicological end-points (DFG, 1972; IPCS, 1986 (neurotoxicity); US EPA, 1986a, 1996a; IARC, 1987; EC, 1992; Health Canada, 1994; IPCS, 1996 (immunotoxicity); IPCS, 1997 (delayed hypersensitivity)). An example (the IARC scheme) is presented in Appendix 1 to illustrate the nature of criteria on which classification of weight of evidence is based. Such classification schemes have been helpful in standardizing and communicating the assessment of hazard identification for particular end-points. In addition to the classifications themselves, narrative statements to summarize the nature of and confidence in the evidence based on limitations and strengths of the database are helpful. Issues that are often addressed include: the nature, reliability, validity and consistency of data on response in humans and in laboratory animals, current knowledge of the mechanistic basis for the response, and, in the absence of human data, the relevance of responses in experimental animals to humans.

The result of the hazard identification exercise is a scientific judgement as to whether the chemical can cause an adverse effect in humans.

The following is intended to provide the reader with an appreciation of the complexity of considerations made in assessing different types of data as a basis for hazard identification in risk assessment. Fundamentals of epidemiology and toxicity testing are not addressed here since they are considered in several other sources. An Environmental Health Criteria monograph on the principles of exposure assessment is currently in preparation (IPCS, in preparation).

Each source of information (e.g., human data, animal data, structure–activity relationships) has its advantages and limitations in contributing to an assessment of weight of evidence, but, collectively, they permit characterization of potential adverse health effects.

3.2 Human data

Well-documented observational and clinical epidemiological studies have the clear advantage over studies in animals in providing the most relevant information on health effects in the species of interest, thus avoiding extrapolation from animals to humans. In addition, epidemiological studies can address hazards to which humans are exposed in their natural environment, in the presence of concomitant risk factors such as diet and smoking.

Human populations are heterogeneous in their composition, and studies of exposed populations are likely to include individuals of differing susceptibility to the chemical of interest. This may be viewed as an advantage relative to toxicological studies, which involve genetically homogeneous populations of test animals.

The database for direct hazard identification in human populations consists primarily of observational (epidemiological) studies and case reports. Some information is also available from ethically conducted human volunteer studies.

In observational studies, the investigator does not control assignment of study subjects to either exposed or non-exposed groups.

Rather, such studies involve investigation of various individuals or groups of subjects as they happen to have been exposed, and at no stage of the study is the exposure of subjects influenced by the research protocol. Although exposure scenarios are more realistic than those in the experimental setting, owing to their observational nature it is often difficult to control for "confounding factors", which may be contributing to the etiology of the disease being investigated. For example, variations in smoking between groups may confound interpretation of observations concerning lung cancer.

Ethical experimental studies in human volunteers offer the advantage of being better able to control for confounding factors. The assignment of study subjects to exposure groups is made by the investigator, who also controls the quality and quantity. Although such investigations are generally reliable for the establishment of both causality and exposure–response relationships, they are most often restricted for ethical reasons to the examination of mild, temporary effects (e.g., neurobehavioural or biochemical changes) of short-term exposures in a limited number of subjects. They have contributed considerably, particularly to our understanding of kinetics and to the development of air quality guidelines and standards for traditional pollutants.

Case reports describe a particular effect in an individual or group of individuals who were exposed to a substance and often observed by a single physician or group of physicians. These reports are often anecdotal or highly selected in nature. Owing primarily to their lack of statistical stability, they are of limited use for hazard assessment, though helpful in generating hypotheses for further study. However, reports of cases of the disease or effect of interest can identify associations, particularly when there are unique features such as an association with a rare disease or effect of interest (e.g., vinyl chloride and angiosarcoma or methylmercury and Minamata disease).

The major types of epidemiological (observational) studies are analytical and descriptive or correlational studies. Each study type has well-known strengths and weaknesses that affect interpretation of study results (Lilienfeld & Lilienfeld, 1979; Mausner & Kramer, 1985; Kelsey et al., 1986; Rothman, 1986). Analytical epidemiological studies (that is, cohort and case-control studies), in which exposure and outcome are examined in individuals rather than in populations, are generally most reliable in hazard identification as a basis for risk

assessment since it is possible to adjust more rigorously for confounding factors. The assessment of results of such studies is based on several features of study design including estimation of exposure, the role of confounding variables and the measurement of outcome. Potential limitations, depending upon the nature of the design, include lack of information on exposure, insufficient sample size, short length of follow-up and potential bias and confounding. These factors may limit the usefulness of particular studies for the purposes of risk assessment.

Epidemiological data demonstrating dose–response, if available, provide an advantageous basis for analysis, since concerns about inter-species extrapolation do not arise. Adequacy of human exposure data for quantification is an important consideration in deciding whether epidemiological data are the best basis for analysis in a particular case. If adequate exposure data exist in a well-designed and well-conducted epidemiological study that detects no effects, it may be possible to obtain an upper estimate of the potential human risk to provide a check on plausibility of available estimates based on animal tumour or other responses (e.g., do confidence limits on one overlap the point estimate of the other?) (Stayner & Bailer, 1993; US EPA 1996a).

3.2.1 Criteria for establishing causality

The first step in the evaluation of results of studies in humans as a basis for hazard identification is the assessment of the individual results of each separate report. The strengths and weaknesses of each study must be considered along with potential for the existence of bias (Gehlbach, 1982), with particular attention to exposure data, criteria for definition of health outcome under study, the size of the study population and the statistical power of the analysis to detect adverse health effects. A set of standardized criteria for assessing the weight of evidence of causality based on assessment of the database has been developed (Hill, 1965; Susser, 1977).

Studies in which there is an apparent absence of evidence for a hypothesized causal relationship between exposure and effect ("negative studies") need to be interpreted carefully (Hernberg, 1980). Such studies should be evaluated for dilution (the inclusion of unexposed people in an allegedly exposed group of persons), misclassification (Copeland et al., 1977), omissions, or premature examination of subjects for diseases that may have long induction

(latency) periods. In addition, the statistical power of the study, i.e. the probability that the study will be able to demonstrate the presence of an effect, such as excessive disease or mortality, in a population if the effect is actually present (Beaumont & Breslow, 1981), must be assessed.

There is no clear-cut criterion to distinguish positive from negative studies. Although statistical significance has often been used as the criteria, most epidemiologists believe that it is overly simplistic to base decisions on arbitrary probability values (Rothman, 1986). For example, when a study fails to detect a statistically significant effect, this may simply reflect inadequate sample size or other aspects of study design. Conversely, when the results of a study are statistically significant, the seemingly positive results may still be due to confounding or even chance.

A positive association between an agent and an effect may be interpreted as implying causality, to a greater or lesser extent, if the following criteria are met: (a) there is not identifiable positive bias; (b) the possibility of positive confounding has been considered; (c) the association is unlikely to be due to chance alone; (d) the association is strong; and (e) there is a dose–response relationship (IARC, 1990). The following criteria for inferring causality from the results of epidemiological studies have been developed by Hill (1965):

(a) The strength of the association as measured by the relative risk

In general, epidemiologists have more confidence in their results when the magnitude of the relative risk is large. However, relative risks of small magnitude do not necessarily imply lack of causality and may be important if the disease under study is common (IARC, 1990). In evaluating relative risks, it is important to note the actual numbers of observed and expected cases.

(b) The consistency of the association

The case for causal inference is strengthened by repetition of findings "by different investigators, in different places, circumstances and times" (Hill, 1965). The reproducibility of findings constitutes one of the strongest arguments for the existence of causality. If there are discordant results among investigations, possible reasons such as differences in exposure should be considered in assessing the results,

and data from studies judged to be of high quality given greater weight than data from studies judged to be methodologically less sound (IARC, 1990).

(c) The temporal relationship between cause and effect

This principle may be simply restated as exposure must precede illness. When latency is a factor, exposures must have occurred sufficiently early to have produced an effect by the time of the study.

(d) The biological gradient of the association

The evidence for causality is strengthened when the risk of disease is shown to increase with levels of exposure. Because there are many possible reasons that an epidemiological study may fail to detect an exposure–response relationship (e.g., poor exposure data, lack of adequate exposure gradient), the absence of a dose–response relationship does not necessarily imply that the relationship is not causal (IARC, 1990). Strong evidence for causality is provided when a change in exposure brings about a change in disease frequency (Hernberg, 1980), e.g., the decrease in risk of lung cancer that follows cessation of smoking (Doll & Hill, 1956).

(e) the specificity of the association

A highly specific association is one in which the disease under study is only induced by a particular agent. Specificity of cause is common in infectious diseases but less common in chronic diseases that often have a multi-factorial etiology. However, a specific association may be observed for certain chronic diseases such as between exposure to crocidolite asbestos and mesothelioma or vinyl chloride and angiosarcoma. Although the presence of specificity seems to imply causality, its absence does not exclude it (Fralick, 1983).

(f) biological plausibility of the association

Hill (1965) stated strongly that a proposed causal relationship should not seriously conflict with knowledge of the biology and pathophysiology of a disease under study. An epidemiological inference of causality may be strengthened by data from experimental studies showing consistency with biological mechanisms. For example, exposure to ionizing radiation causes cancer in many animal

species. However, the lack of mechanistic or positive animal bioassay data to support an association observed in an epidemiological study is not, in itself, sufficient reason to reject causality.

3.3 Animal studies

Owing to the lack of adequate epidemiological data for most substances, toxicological studies in animal species play an important role in hazard identification for risk assessment. Toxicity studies vary widely in purpose, design and conduct, and range from relatively well-standardized and widely accepted test methods for assaying various types of toxicity to large numbers of basically research-oriented investigations employing specialized study designs.

The design, conduct and completeness of reporting of experimental findings in toxicological studies on mammalian species are of critical importance in determining the validity and relevance of results. Toxicological results from adequate animal systems signal anticipated effects in humans. Thus, negative results cannot be assessed from an inadequate study, and full evaluation of a positive effect is confounded by incomplete reporting from poorly designed or poorly conducted studies. However, positive findings cannot be ignored. Studies should be of good scientific quality and follow standard guidelines and recognized good laboratory practices (GLPs) wherever possible.

Information on the design of specific bioassays, including those that address acute, short-term, sub-chronic, chronic and developmental and reproductive toxicity, immunotoxicity and carcinogenicity, are not presented here but are available in test guidelines, for which principles of GLP are also specified (IARC, 1986; OECD, 1987, 1998; Chhabra et al., 1990). A list of currently available OECD Guidelines is included in Appendix 2. In this section, examples of factors to be taken into account in assessing these various aspects of study design for hazard identification are described.

Major end-points in toxicity studies can be grouped into the following categories (IPCS, 1987a):

- Functional manifestations (weight loss, laxative effects, etc.);
- non-neoplastic lesions with morphological manifestations/organ-directed toxic effects;
- neoplastic/carcinogenic manifestations.

In addition, a number of specific end-points may require targeted testing strategies. Such end-points include skin and eye irritation, reproductive/developmental manifestations, immunotoxicity and neurotoxicity (including neurodevelopmental effects).

It is important to recognize that there are two types of data generated in such studies; those in which response is graded, such as enzyme inhibition (i.e. continuous data), and those in which the response occurs or does not occur in a single animal, such as a particular tumour (i.e. quantal data).

In assessing the relevance of various toxicological studies to hazard identification and risk assessment, several features of study design are considered, including the purity of the compound administered, physico-chemical properties (volatility, stability, solubility), homogeneity of distribution in inhalation experiments, the size of the study (i.e. the number of exposed and control animals), whether the study adhered to the principles of GLP, the relevance of the route of exposure to that of humans, duration of exposure, the number and suitability of the dose levels administered, the extent of examination of various toxicological end-points and the statistical analysis of the data. The types, site, incidence and severity of effects and the nature of the exposure– or dose–response relationship are also taken into account. Where data indicate that there are significant differences in absorption, distribution, metabolism and elimination of the compound in different animal species, wherever possible, studies in which the species and strain of animal are most similar to *Homo sapiens* in this regard are used (where relevant human data are available). The consistency of the results of the principal studies are also considered in the assessment of the weight of evidence for an effect (e.g., whether similar effects have been observed in studies in other species or whether such effects would have been expected based on the structure or properties of the chemical).

For example, the size of each exposure and concurrent control group should be large enough for thorough toxicological and statistical evaluation. The number of animals considered sufficient depends on the variability, sensitivity and nature (e.g., quantal or continuous) of the end-point being evaluated. For example, it is commonly 50 per group in carcinogenicity bioassays where the responses of interest are quantal in nature and 10 per group in subchronic studies, where many of the examined end-points are continuous.

Studies in which the route of exposure is similar to that of humans are most relevant to hazard identification for risk assessment. For substances of low toxicity, it is important to ensure that when administered in the diet, the quantities of the substance do not interfere with normal nutritional needs.

Studies designed and conducted with 3–5 dosed groups plus a vehicle control group of animals will yield reasonable dose–response data relevant to hazard identification. The highest concentration of the chemical should be one that induces a recognizable effect in the animals such as changes in body or organ weights, enzyme changes or minor histological changes. Changes such as mortality, gross pathological changes, and painful or stressful conditions should be avoided as they may confound the results of the study and may not be in compliance with national and local animal welfare regulations. Intermediate dose(s) should be targeted to produce minimally observable toxic effects. Dose levels should be selected to produce graded responses; too large intervals may complicate accurate estimations of the lowest-observed-effect level (LOEL). Ideally, the lowest dose should not demonstrate any toxicity (e.g., a NOAEL).

To assess fully the toxicological potential of a chemical for local and systemic effects, all major organ systems should be examined for dose–related effects and adverse effects in various organs should be evaluated and described.

3.4 *In vitro* studies

Isolated cells, tissues and organs can be prepared and maintained in culture by methods that preserve their *in vivo* properties and characteristics. Increasing concern about the ethics of animal experimentation has served to catalyse efforts leading to the possible replacement or reduction in the use of animals, and the refinement of test methods to minimize the stress and suffering to animals (ECETOC, 1989; Gelbke, 1993). *In vitro* testing contributes particularly to the assessment of genotoxicity, permitting a decision concerning the need for further testing.

Over the last decade, *in vitro* tests have been proposed as a prescreen or as an alternative method for other end-points, such as prenatal toxicity, eye irritation, dermal irritation, tumour promotion and target organ toxicity (Purchase, 1986; Tennant et al., 1987;

Anderson, 1990; Frazier, 1993; Atterwill, 1995). There has been particular emphasis on validation programmes for skin and eye irritation, but most of the tests mentioned above have not yet been sufficiently validated and the results of validation studies, especially in the past, have been lacking in consistency. The results have failed to meet the need for reproducibility and high correlation, ideally with sound human data but usually, for practical reasons, with existing animal tests, which they are intended to replace.

Aspects that are important in assessing the adequacy of *in vitro* studies include:

- the range of exposure levels, taking into account the toxicity of the substance in the bacteria/cells, its solubility and, where appropriate, its effects on the pH and osmolality of the culture medium;
- whether, in the case of volatile substances, precautions were taken to ensure the maintenance of effective concentrations of the substance in the test medium;
- whether (when necessary) an appropriate exogenous metabolism mix (e.g., S9 from induced rat or hamster liver) was used;
- whether appropriate negative and positive controls were included; and
- whether there was an adequate number of replicates (within the tests and of the tests).

Clearly, greater mechanistic understanding would facilitate moving from purely empirical/correlative approaches to more mechanistic-based tests. This is likely to facilitate greatly the chances of adequate validation and acceptance of alternatives for regulatory purposes.

3.5 Structure–activity relationships

Where epidemiological and toxicological data are not available, the use of structure–activity relationships (SARs) may be considered. SARs are based on the assumption that chemical substances that reach

and interact with target sites by the same mechanism do so as a result of their similar chemical properties.

At present, SAR techniques, particularly those of a quantitative nature, are not well developed in relation to mammalian toxicity. They are primarily of value in predicting toxicokinetic properties and in priority setting for research and evaluation.

4. DOSE–RESPONSE

4.1 Introduction

Approaches to quantification of dose–response vary according to the scope and purpose of assessments. However, for most types of toxic effects (i.e. organ-specific, neurological/behavioural, immunological, non-genotoxic carcinogenesis, reproductive or developmental), it is generally considered that there is a dose or concentration below which adverse effects will not occur (i.e. a threshold). For other types of toxic effects, it is assumed that there is some probability of harm at any level of exposure (i.e. that no threshold exists); this currently applies primarily for mutagenesis and carcinogenesis. Some have restricted the non-threshold assumption to genotoxic carcinogens.

The distinction in approaches for genotoxic carcinogens and other types of toxic effects is based primarily on the premise that simple events such as *in vitro* activation and covalent binding may be linear over many orders of magnitude. Though it is not possible to demonstrate experimentally the presence or absence of a threshold, differences in approach to the dose–response assessment of genotoxic versus non-genotoxic carcinogens have been adopted in some countries. However, simple pragmatic distinction on this basis is increasingly problematic. For example, it is likely that there are thresholds for aneugenic genotoxic effects.

If a threshold has been assumed (e.g., for non-neoplastic effects and non-genotoxic carcinogens), traditionally, a level of exposure below which it is believed that there are no adverse effects, based on a no-observed-adverse-effect level or NOAEL (approximation of the threshold) and uncertainty factors, has been estimated (section 4.3). Alternatively, the magnitude by which the N(L)OAEL exceeds the estimated exposure (i.e. the "margin of safety"), is considered in light of various sources of uncertainty (Commission Regulation (EC) No. 1488/94; Council Regulation (EEC) 793/93) (EC, 1993, 1994). In the past, this approach has often been described as "safety evaluation". Therefore, the dose that can be considered as a first approximation of the threshold, i.e. the NOAEL, is critical. Increasingly, however, the "benchmark dose", a model-derived estimate (or its lower confidence limit) of a particular incidence level (e.g., 5%) for the critical effect,

is being proposed for use in quantitative assessment of the dose–response for such effects.

At present, there is no clear consensus on appropriate methodology for the risk assessment of chemicals for which the critical effect may not have a threshold (i.e. genotoxic carcinogens and germ cell mutagens). Indeed, a number of approaches based largely on characterization of dose–response have been adopted for assessment in such cases (section 4.4). Therefore, the critical data points are those that define the slope of the dose–response relationship (rather than the NOAEL, which is the first approximation of a threshold).

In North America and some European countries, cancer risks have traditionally been assessed by mathematical modelling of the dose–response data in the observable range to estimate the risk at much lower human intakes or exposures (low dose risk extrapolation). It should be noted, however, that quantitative estimation of such risks, particularly those orders of magnitude below the experimental range (i.e. low dose risk estimation), is uncertain. Owing to this uncertainty, some countries have chosen not to adopt this approach as the basis for their regulatory actions for genotoxic carcinogens, and other countries are increasingly adopting alternative measures of dose–response. In Canada and the USA, for example, there is, currently, increasing reliance on specification of the margin between potency in the experimental range and exposure as the measure of risk for carcinogens (Health Canada, 1994; US EPA, 1996b). In the United Kingdom, dose–response for genotoxic carcinogens is not quantified; instead the goal in risk management is to eliminate exposure or to reduce levels to as low as is reasonably practical (UK DOH, 1991).

Owing to the increasing reliance on modelling in the experimental range to characterize dose–response for tumours, which is essentially similar to the benchmark dose being used increasingly to characterize dose–response for non-neoplastic effects, approaches to quantitative risk estimation for carcinogenic and non-neoplastic effects are converging.

4.2 Considerations in dose–response assessment

4.2.1 Introduction

In considering toxic effects at various dose levels, the dose range of interest is generally the low-dose range, since it usually reflects the human exposure situation. Often, however, data on dose–response are available for higher doses only, and are often derived from animal experiments only. Therefore, the uncertainty in the dose–response assessment is larger than the uncertainty in hazard identification, as it requires extrapolation both from animal to human and from high-dose to low-dose levels. In certain instances, a distinction is made between response and effect, with a response being quantal and counted (e.g., the incidence of a tumour) and an effect being graded and measured (e.g., relative liver weight).

4.2.2 Inter- and intra-species considerations

4.2.2.1 Introduction

The strains and species of laboratory animals exposed in toxicity studies have been selected to show minimum inter-individual variability. In contrast to laboratory animals, humans represent a very heterogeneous population with both genetic and acquired diversity.

Therefore, two principal areas are considered when interpreting data on toxicity acquired in animal species in relation to human risk:

a) *Inter-species consideration*: comparison of the data for animals with a representative healthy human. Species differences result from metabolic, functional and structural variations.

b) *Intra-species or inter-individual consideration*: comparison of the representative healthy human with the range of variability present within the human population in relation to the relevant parameter(s).

For each of these areas, there are two aspects to be considered in assessing risk, i.e. toxicokinetics (the delivery of the compound to the site of action) and toxicodynamics (the inherent sensitivity of the site of action to the chemical). Any approach that allows for the incorporation of adequate data on toxicokinetic or toxicodynamic

differences between test animal and humans, or between different humans, will increase the scientific validity of risk assessment.

Sources of inter-species and inter-individual variations in toxicokinetics include differences in anatomy (e.g., gastrointestinal structure and function), physiological function (e.g., cardiac output, renal and hepatic blood, glomerular filtration rate and gastric pH), and biochemical differences in, for example, enzymes involved in xenobiotic metabolism. Sources of inter-species and inter-individual differences in toxicodynamics (or inherent sensitivity) also include anatomy. For example, the effect may occur in an organ of questionable relevance to humans, such as the rodent forestomach. Physiological differences, such as the hormonal control of the target organ, and biochemical differences, e.g., species differences in key biochemical components such as α2u-globulin, may also play a role (Flamm & Lehman-McKeeman, 1991).

In some cases, it may be possible to conclude that effects detected in animals are unlikely to be relevant to humans. In other cases, there may be data to indicate that humans are likely to be more or less sensitive than animal species; this information is important for consideration in selection of critical effects.

If compound-specific toxicokinetic data are introduced into risk assessment, then it is essential that these are related to the species, protocol and active chemical entity (e.g., parent compound or metabolite) involved in the toxicity that is the basis for the hazard identification (Monro, 1990, 1993; Renwick, 1993a).

4.2.2.2 *Species differences*

Metabolism and structural/functional variations are both important determinants of species differences. Common areas of metabolic variation between species are digestive tract enzymes, levels of circulating enzymes, liver enzymes and detoxification processes.

In extrapolating between species, three aspects need to be considered: the first relates to differences in body size, which requires dose normalization or scaling (often done by expressing the dose per kg body weight). The second relates to differences in toxicokinetics, particularly bioactivation and/or detoxification processes. The third aspect concerns the nature and severity of the target for toxicity.

Inter-species normalization (or scaling) is generally based on physical characteristics (e.g., body weight, body surface area), although occasionally it is based on caloric demand or, where there are data in four species, multiple species regression.

When clearance of the parent substance is limited by enzyme activity rather than blood flow or when metabolites are the toxic agents, more sophisticated physiologically based pharmacokinetic models are more appropriate, provided that adequate data are available. Currently, such data are available for only a small number of substances.

4.2.2.3 *Human variability*

Although data from animal studies may provide limited information on inter-individual variability within the test species, it is the greater potential variability in the human population that must be addressed in risk assessment. Sources of inter-individual variability in human populations include, for example, variations in genetic composition, nutrition, disease state and lifestyle.

Inter-individual variability may occur in both the toxicokinetics of the chemical and the sensitivity of the target for toxicity.

4.3 Non-neoplastic (threshold) effects

Although specific aspects vary, comparable schemes have been developed by various national and international agencies and organizations to derive levels of exposure considered to present minimal or no risk for non-neoplastic effects to the general population. These include: Reference Dose/Concentrations (US Environmental Protection Agency), Tolerable Daily Intakes/Concentrations (Health Canada), Minimal Risk Levels (US ATSDR), Tolerable/Acceptable Daily Intakes (IPCS, 1987a,b, 1990a,b, 1994). In evaluating dose–response for non-neoplastic effects, the European Union does not derive tolerable intakes; instead effect levels are compared to estimated exposures ("margin of safety").

In the case of substances for which the critical effect is not carcinogenicity, it is generally assumed that there is a level of exposure below which the probability for an adverse effect to occur is minimal, if not zero (i.e. a threshold). The mechanism underlying this

assumption is that multiple cells (or cell components) must be irreversibly injured before an adverse effect becomes evident, and that cellular defence and repair mechanisms are overwhelmed by the rate at which injury occurs.

4.3.1 Characterization of threshold

For toxic effects, other than heritable mutations and genotoxic carcinogenicity, considered to have a threshold, i.e. a dose below which there would be no detectable effect, a number of different estimates may be used as an approximation of the biological threshold.

4.3.1.1 *No-observed-adverse-effect level (NOAEL)*

This is a simple estimate of the highest dose in which the incidence of a toxic effect or change in target organ weight, histopathology etc., was not significantly different from the untreated group (from a statistical and biological assessment). It is based on toxic effects of functional importance or pathological significance rather than adaptive responses, and is defined as the highest observed dose or concentration of a substance at which there is no detectable adverse alteration of morphology, functional capacity, growth, development or life span of the target (IPCS, 1994). The NOAEL will depend on the sensitivity of the methods used, the sizes of the exposed groups and the differences between estimated exposures or doses. The NOAEL is an observed value which does not take into account the nature or steepness of the dose–response curve.

In consequence, the NOAEL is not the same as the biological threshold and may either underestimate or overestimate the true no-effect level. Though such limitations are recognized and have been the basis for criticism of the use of the NOAEL (Leisenring & Ryan, 1992; Calabrese & Baldwin, 1994), dose–response relationships are often so poorly characterized that the NOAEL or LOAEL is the only quantitative value available as the basis for characterization of dose–response.

4.3.1.2 *Benchmark dose/concentration*

This is an alternative method of defining the lower end of the dose–response curve in the area of the observed threshold (Crump, 1984). The benchmark dose is the effective dose (or its lower confidence limit) that produces a certain increase in incidence above

control levels (e.g., 1% or 5% of the maximum toxic response). The benchmark dose is derived by modelling the data in the observed range and selecting the point on the curve (or its upper confidence limit) corresponding to a specified increase in the incidence of an effect. Any model that fits the empirical data well is likely to provide a reasonable estimate of the benchmark dose, and choice of the model may not be critical since estimation is within the observed dose range. The advantages of the benchmark dose are that it takes into account the slope of the dose–response curve, the size of the study groups and the variability in the data. It should be recognized that unless there are a sufficient number of dose levels at which effects have been observed, the benchmark dose/concentration offers little advantage over effect levels as an approximation of the biological threshold. Statistical modelling of continuous data as a basis for developing benchmark doses/concentrations is also currently problematic.

4.3.1.3 *Lowest-observed-adverse-effect level (LOAEL)*

In some studies, there is a significant effect compared to controls in the lowest dose group. In such cases, there is no NOAEL and an alternative approach must be adopted. These include estimation of a benchmark dose or threshold estimate (if the dose–response data approach zero response) or application of an additional uncertainty factor.

4.3.2 *Uncertainty factors*

In deriving tolerable intakes (or RFDs or ADIs), the N(L)OAEL or benchmark dose/concentrations are divided by uncertainty factors to account for variabilities and uncertainties. Principal factors applied relate to extrapolation from animal studies to the human situation and to inter-individual variability within the response for the human population. Traditionally, default factors of 10 have been applied to account for each of these variations. Additional uncertainty factors have been applied to account for the inadequacy of the database, for extrapolation from subchronic to chronic exposure and from LOAEL to NOAEL, and for the severity of a given effect.

Knowledge of actual inter-species differences and inter-individual variability in the biokinetic behaviour of a given compound (toxicokinetics) and its target organ (toxicodynamics) would enable the development of full biologically based dose–response models or

physiologically based pharmacokinetic models. In the absence of full biological understanding, several approaches have been developed to incorporate as much scientific information as possible in the development and application of uncertainty factors. Indeed, a formal approach to the development of data-derived uncertainty factors has been developed by Renwick (1993a,b) and proposed by IPCS (IPCS, 1994). It is presented here as an example of a flexible but structured approach to the selection of uncertainty factors which reflects the nature and extent of the database (Lewis, et al., 1990; Renwick, 1993b).

The scheme retains the two 10-fold default uncertainty factors (for inter-species and inter-individual variation) as the cornerstone of the structure, in the absence of specific and relevant data on toxicokinetics or mechanism of action (Renwick, 1993a). However, it allows for the division of the two default uncertainty factors (for inter- and intra-species variation) to account for toxicokinetics and toxicodynamics. The default components of these two factors can then be replaced by actual quantitative data, when available. This reduces the extent of uncertainty by allowing the incorporation of appropriate data on the compound of interest in one or both of these aspects, where they exist (Fig. 1). There would be very few databases in which adequate information was available to account quantitatively for both aspects of either inter-species or of inter-individual differences. Incorporation of data on one aspect only (e.g., inter-species toxicokinetics) requires the use of a default factor for the uncertainty associated with the remaining undefined aspect (e.g., inter-species toxicodynamics).

Uncertainty factors often address:

a) Nature of toxicity

Some bodies, e.g., the FAO/WHO Joint Meeting on Pesticide Residues (JMPR), have used an additional "safety factor" in cases where the NOAEL is derived for a critical effect that is a severe and irreversible phenomenon, such as teratogenicity or non-genotoxic carcinogenicity, especially if the dose–response relationship is shallow (IPCS, 1987a,b, 1990a,b). This additional factor (of up to 10) has been applied in such cases to provide a greater margin between the intake/exposure of any particularly susceptible humans and the dose–response curve for such toxicity demonstrable in animals. However,

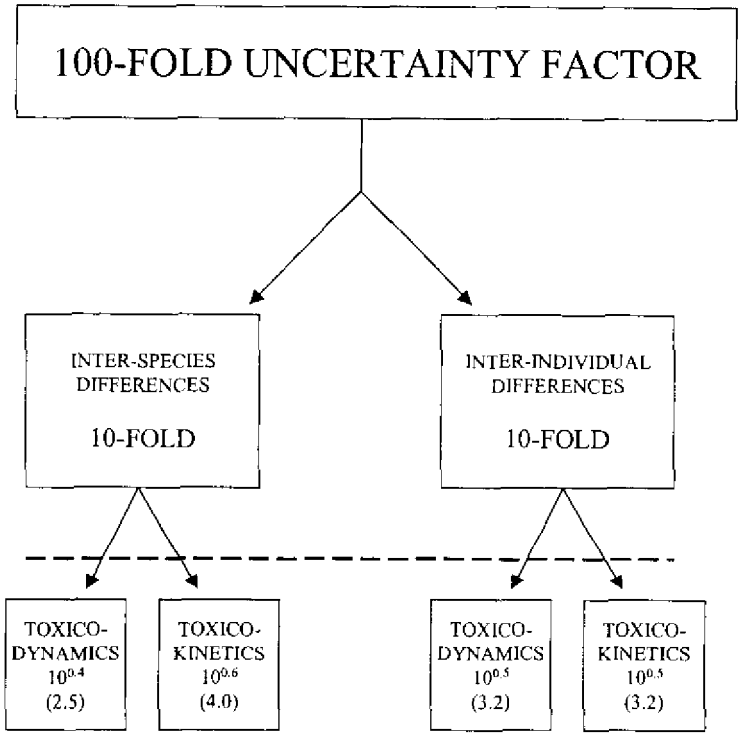

Fig. 1. Subdivision of the 100-fold uncertainty factor showing the relationship between the use of uncertainty factors (above the dashed line) and proposed subdivisions based on toxicokinetics and toxicodynamics (based on Renwick, 1993b). Actual data should be used to replace the default values if available.

for other types of toxic effect, for example, changes in organ weight or histopathology, a value of 1 (no further correction) would be appropriate.

b) Adequacy of the database

A minimum dataset that is considered adequate for risk assessment is generally established. This will vary according to the purpose of the assessment (e.g., screening level or full). Additional deficiencies in a toxicity database that increase the uncertainty of the extrapolation

process have also been recognized by the use of an additional uncertainty factor. A value of 1 would be applied to an appropriate and complete database, but a higher factor would be considered necessary for barely adequate databases.

c) LOAEL to NOAEL extrapolation

In situations where a NOAEL has not been achieved but data are of sufficient quality to be the basis of the risk assessment, then an extra uncertainty factor may be applied (Dourson & Stara, 1983). The magnitude of this factor (e.g., 3 or 10) should be based on the dose–response data.

d) Inter-species extrapolation

The inter-species uncertainty factor is not necessary if the NOAEL or risk assessment is based on human data. Where an assessment is based on data in animals, however, and in situations where there are appropriate compound-specific toxicokinetic and/or toxicodynamic data, the relevant default uncertainty factor for inter-species variation would be replaced by the data-derived factor (Renwick, 1993b). Data on physiologically based pharmacokinetic (PBPK) modelling should be included wherever possible; however, such information is available currently for only a small number of substances. If a data-derived factor is introduced, then the commonly used 10-fold factor would be replaced by the product of that factor and the remaining default factor.

The composite default value of 10 has been criticized as inadequate, for example, to allow for metabolic processes in mice which can be related to body surface area (Calabrese et al., 1992); the introduction of data-derived uncertainty factors would allow the logical future development of more appropriate species specific defaults.

e) Inter-individual variability in humans

In situations where appropriate toxicokinetic and toxicodynamic data exist for a particular compound in humans, then the relevant uncertainty factor should be replaced by the data-derived factor (Renwick, 1993b). Data on PBPK modelling may also be able to contribute to this assessment. If a data-derived factor is introduced,

then the commonly used 10-fold factor would be replaced by the product of the data-derived factor and the remaining default factor.

Although the 10-fold default uncertainty factor is reasonable for most cases (Dourson & Stara, 1983), it has been criticised as inadequate for human variability especially when genetically determined differences in a bioactivation process may be involved (Calabrese, 1985; Goldstein, 1990). This concern reinforces the importance of using an approach that allows the incorporation of data on human variability in either toxicokinetics of the compound or the sensitivity to its mechanism of action.

In addition to approaches aimed at incorporating as much biological data as possible in the derivation of uncertainty factors, probabilistic approaches have been investigated for the characterization of uncertainty (Baird et al., 1996; Price et al., 1997). Distributions can be developed on the basis of empirical relationships observed for, for example, variations between LOAELs and NOAELs and effect levels in subchronic versus chronic studies. Monte Carlo techniques can be used to integrate probabilities for the various areas of uncertainty.

4.4 Quantitative risk assessment for neoplastic (non-threshold) effects

4.4.1 *Introduction*

A number of approaches have been adopted for characterization of dose–response in the assessment of genotoxic neoplastic effects, including quantitative extrapolation by mathematical modelling of the dose–response curve to estimate the risk at likely human intakes or exposures (low-dose risk extrapolation). Traditionally, where dose–response has been extrapolated into the low-dose range, this has been accomplished by the use of the linearized Armitage-Doll multi-stage model. Dose–response may also be estimated in a two-step process by straight linear extrapolation into the low-dose range from a modelled point on the dose–response curve. Other measures of dose–response include estimation of carcinogenic potency in the experimental range and division of effect levels by a margin of protection. In more recently developed biological models, different stages in the process of carcinogenesis have been incorporated and time to tumour has been taken into account (Moolgavkar et al., 1988), although currently data

are sufficient for application in only a limited number of cases. In some cases where data permit, the dose delivered to the target tissue has been incorporated into the dose–response analysis (PBPK modelling) (IPCS, 1993).

In the same way as approaches adopted for non-neoplastic (threshold) effects, there are increasingly attempts to incorporate more of the scientific data in adopted approaches. For example, the proposed cancer guidelines issued by the US EPA (1996b), updating the previous guidelines (US EPA, 1986a), put emphasis on the full integration of mechanistic information and dose–response data. Depending on the mode of action, linear extrapolation into the low-dose range or, alternatively, a margin of exposure would be presented. The adequacy of the latter approach must be judged by criteria similar to those used in developing tolerable intakes/exposures for non-cancer effects.

4.4.2 *Linear extrapolation*

Where data on the mechanism of tumour induction are not available, as a default, risks are often linearly extrapolated into the low-dose range. Previously (e.g., US EPA, 1986a) the linearized multistage model was widely adopted for such extrapolations for data from studies in animal species, whereas data from epidemiological studies were generally modelled using a multistage model with a linear term. More recently, curve fitting within the range of observation with extrapolation from the lower 95% confidence limits on a dose associated with a 10% extra risk (the LED_{10}) has been recommended (US EPA, 1996a). Linear extrapolation is considered to be appropriate if available evidence supports a mode of action that is anticipated to be linear or, as a science policy default, there is no evidence of either linearity or non-linearity.

Other approaches to linear extrapolation have been described in the literature. Gross et al. (1970) suggested a method based on discarding data at the upper end of the dose range until a linear model provides an adequate description of the remaining data. Van Ryzin (1980) suggested the use of any model that fits the data reasonably well to estimate the dose producing an excess risk of 1%, and then using simple linear extrapolation to lower doses. Gaylor & Kodell (1980) proposed fitting a model to the available data and then using linear extrapolation below the lowest dose at which observations were

taken. Since the estimates at the lower doses might be unduly influenced by the choice of the model used in the experimental dose range, Farmer et al. (1982) suggested linear extrapolation below the lowest dose or the dose corresponding to an estimated risk of 1%, whichever was larger.

A model-free procedure based on linear extrapolation below the lowest dose showing an increased (not necessarily statistically significant) risk has been proposed by Krewski et al. (1984, 1986) using linear extrapolation from all doses for which there were no statistically significant increases in tumour incidence above the baseline level, and selecting the smallest slope for low-dose risk estimation. Similarly, Gaylor (1987) considered the smallest slope obtained from all the possible combinations of data from the doses where the lowest dose was in the convex portion of the dose–response curve. In both cases, upper confidence limits on the slopes were used.

A number of arguments have been advanced in support of the hypothesis of low-dose linearity (Krewski et al., 1986; Murdoch et al., 1987). For example, the class of additive background models considered by Crump et al. (1976) predicts low-dose linearity provided only that the response increases smoothly with dose. However, it is difficult to prove or disprove low-dose linearity experimentally even in bioassays involving extremely large numbers of animals (Gaylor et al., 1985). Indeed, dose–response curves for different types of tumours in mice following exposure to 2-acetylaminofluorene (2-AAF) in an ED_{01} study varied considerably.

Often, linear extrapolation is criticized as being too conservative. For example, Bailar et al. (1988) demonstrated that a significant fraction of bioassays conducted for the National Toxicology Program indicate that, at high experimental doses, observed response rates are higher than those predicted by a linear model. They argue that, at low doses, the one-hit model may thus not be conservative in some cases. However, these observations are not necessarily inconsistent since, at low doses, the linear term predominates. Crump et al. (1976), Peto (1978) and Hoel (1980) argue that low-dose linearity occurs when substances augment existing carcinogenic processes. The formation of DNA adducts, which may be predictive of certain tumours induced by genotoxic carcinogens, has often been observed to be linear at very low doses (Poirier & Beland, 1987). Based on these considerations, it

is unclear whether an estimate based on a linear approximation over- or under-estimates the true risk.

The outcome of low-dose extrapolation is the resulting lifetime cancer risk associated with estimated exposure for a particular population. In view of the considerable uncertainties in extrapolating results over several orders of magnitude, in the absence of information on mechanisms of tumour induction, specification of risks in terms of predicted incidence or numbers of excess deaths per unit of the population implies a degree of precision that is considered misleading by some (e.g., Health Canada, 1994).

4.4.3 Estimation of potency in the experimental range

For assessment of Priority Substances under the Canadian Environmental Protection Act (CEPA), e.g., for genotoxic carcinogens, a Tumorigenic Dose or Concentration$_{05}$ (TD_5) has been adopted as the measure of dose–response (Health Canada, 1994; Meek et al., 1994). It is the intake or concentration associated with a 5% incidence of tumours in experimental studies on animals or epidemiological studies on human populations. It serves as the basis for development of an Exposure/Potency Index (EPI) which is the estimated daily human intake or exposure divided by the TD_5. A calculated EPI of 10^{-6} represents a one million fold difference between human exposure and that at the lower end of the dose–response curve, on which the estimate of potency is based.

Any model that fits the empirical data well is likely to provide a reasonable estimate of the TD_5. Choice of the model may not be critical since estimation is within the observed dose range, thereby avoiding the numerous uncertainties associated with low-dose extrapolation. Wherever possible, and if considered appropriate, information on pharmacokinetics, metabolism and mechanisms of carcinogenicity and mutagenicity is incorporated into the quantitative estimates of potency derived particularly from studies in animals (to provide relevant scaling of potency for human populations). The value of 5% is arbitrary; selection of another value would not affect the relative potencies for each of a range of compounds. Indeed, in the literature, others have proposed the TD_{50} (Peto et al., 1984) and the TD_{25} (Allen et al., 1988; Dybing & Huitfeldt, 1992; Dybing et al., 1997). The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment in the United Kingdom has

concluded that the TD_{50} is the most practical quantitative estimate of carcinogenic potency for the ranking of genotoxic carcinogens (UK DOH, 1995).

If there is no evidence for linearity, and there is sufficient evidence to support an assumption of non-linearity for the carcinogenic response, US EPA (1996a) recommends estimation of a margin of exposure, which is the LED_{10} or other point of departure divided by the environmental exposure of interest. It should be noted, however, that this contrasts with the approach in Canada and Europe, where characterization of potency within the experimental range is considered appropriate for carcinogens, whereas the default in the USA is linear. Indeed the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment in the United Kingdom concluded that potency indices are not appropriate for the ranking of non-genotoxic carcinogens. Rather for non-genotoxic compounds, the emphasis should be on understanding mechanisms and their relevance to humans.

4.4.4 Two-stage clonal expansion model

This approach is based on the two-stage model of carcinogenesis, in which it is hypothesized that chemical carcinogenesis occurs in two steps. Cells are initiated following the occurrence of genetic damage in one or more cells in the target tissue. Such initiated cells may then undergo malignant transformation to give rise to a cancerous lesion. The rate of occurrence of such lesions may be increased by subsequent exposure to a promoter, which serves to increase the pool of initiated cells through mechanisms that result in clonal expansion.

Mathematical formulations of this process have been presented by Moolgavkar et al. (1988) and Chen & Farland (1991). This stochastic birth–death–mutation model assumes that two mutations, each occurring at the time of cell division, are necessary for a normal cell to become malignant. Initiating activity may be quantified in terms of the rate of occurrence of the first mutation. The overall rate of occurrence of the second mutation describes progression to a fully differentiated cancerous lesion. Promotional activity is measured by the difference in the birth and death rates of initiated cells. In the absence of promotional effects and variability in the pool of normal cells, the two-stage birth–death–mutation model reduces to the classical two-stage model.

It should be noted, however, that there are currently few cases where data are sufficient to permit application of such a model.

4.4.5 Proportional analyses – carcinogenic and non-neoplastic effects

There have been several investigations of the possibility of predicting potency for particular types of toxicity from data on other types of toxicity, including work by Tennant et al. (1987), Portier (1988), Travis et al. (1990a,b, 1991), Zeiger et al. (1990) and Haseman & Clark (1990). Such approaches have been necessary due, for example, to the high cost and degree of difficulty of long-term or carcinogenic bioassays. However, it is important to note that correlations between potencies for different types of effects may be artificially strengthened by dose selection (e.g., the top dose in carcinogenic bioassays is often the maximum tolerated dose, selected to elicit small reductions in body weight).

5. EXPOSURE ASSESSMENT

The objective of exposure assessment is to determine the nature and extent of contact with chemical substances experienced or anticipated under different conditions. Approaches for assessing exposure and characterizing uncertainties/variability in resulting estimates presented here are derived primarily from the Exposure Assessment Guidelines (US EPA, 1986b, 1992).

5.1 Definition of exposure and related terms

Although there is reasonable agreement that human exposure means contact with the chemical or agent (Allaby, 1983; Environ, 1988; Hodgson et al., 1988), there has not yet been widespread agreement as to whether this means contact with (a) the visible exterior of the person (skin and openings into the body such as mouth and nostrils), or (b) the so-called exchange boundaries where absorption takes place (skin, lung, gastrointestinal tract). These different definitions have led to some ambiguity in the use of terms and units for quantifying exposure. In 1992, The US EPA published Guidelines (US EPA, 1992) defining exposure as taking place at the visible external boundary, as in (a) above.

Under this definition, it is helpful to think of the human body as having a hypothetical outer boundary separating inside the body from outside the body. This outer boundary of the body is the skin and the openings into the body such as the mouth, the nostrils, and punctures and lesions in the skin. Exposure to a chemical is the contact of that chemical with the outer boundary. An exposure assessment is the quantitative or qualitative evaluation of that contact, which includes consideration of the intensity, frequency and duration of contact, the route of exposure (e.g., dermal, oral or respiratory), rates (chemical intake or uptake rates), the resulting amount that actually crosses the boundary (a dose), and the amount absorbed (internal dose). The Commission of the European Communities (EC, 1996) presented a similar definition for exposure assessment: the determination of the emissions, pathways and rates of movement of a substance and its transformation or degradation, in order to estimate the concentrations/ doses to which human populations or environmental spheres (water, soil and air) are or may be exposed.

Depending on the purpose of an exposure assessment, the numerical output may be an estimate of the intensity, rate, duration and frequency of contact exposure or dose (the resulting amount that actually crosses the boundary). For risk assessments based on dose–response relationships, the output usually includes an estimate of dose.

5.2 Exposure and dose

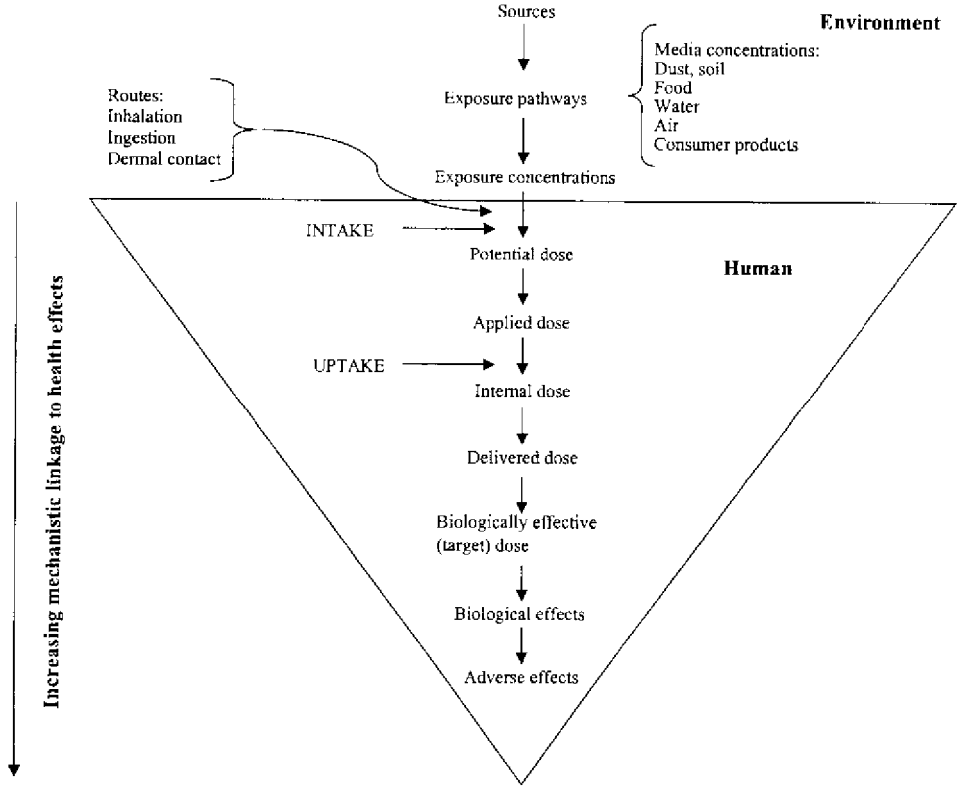

Fig. 2. Environmental health paradigm showing the role of exposure (adapted from Sexton et al. (1995) and IPCS (1993))

Most of the time, the chemical coming into contact with the outer boundary of the body is contained in air, water, soil, a product or a transport or carrier medium; the chemical concentration in these media at the point of contact is the concentration, on which exposure estimates are based. Exposure over a period of time can be represented by a time-dependent profile of the exposure concentration. The area under the curve of this profile is the magnitude of the exposure, in concentration–time units (Lioy, 1990; US NRC, 1990):

$$E = \int_{t_1}^{t_2} C(t)\ dt \qquad (1)$$

where E is the magnitude of exposure, C(t) is the exposure concentration as a function of time, and t is time, t_2–t_1 being the exposure duration (ED). If ED is a continuous period of time (e.g., a day, week, year, etc.), then C(t) may be zero during part of this time. Integrated exposures are done typically for a single individual, a specific chemical, and a particular pathway or exposure route over a given time period.

The integrated exposures for a number of different individuals (a population or population segment, for example), may then be displayed in a histogram or curve (usually, with integrated exposure increasing along the abscissa or x-axis, and the number of individuals at that integrated exposure increasing along the ordinate or y-axis). This histogram or curve is a presentation of an exposure distribution for that population or population segment.

Applied dose is the amount of a chemical at the absorption barrier (skin, lung, gastrointestinal tract) available for absorption. Usually, it is very difficult to measure the applied dose directly, as many of the absorption barriers are internal to the human and are not localized in such a way as to make measurement easy. An approximation of applied dose can be made, however, using the concept of potential dose (Lioy, 1990; US NRC, 1990). Potential dose is simply the amount of the chemical ingested, inhaled or in material applied to the skin.

For the dermal route, potential dose is the amount of chemical applied or the amount of chemical in the medium applied, e.g., as a small amount of particulate deposited on the skin. It should be noted

that as not all of the chemical in the particulate is in contact with the skin, this differs from exposure (the concentration in the particulate multiplied by the time of contact) and applied dose (the amount in the layer actually touching the skin).

The applied dose, or the amount that reaches the exchange boundaries of the skin, lung or gastrointestinal tract, may often be less than the potential dose if the material is only partly bioavailable. This will depend, for example, on the form in which the compound is administered (e.g., neat or in vehicle on skin). Where data on bioavailability are known, adjustments to the potential dose to convert it to applied dose and internal dose may be made. For example, chemicals reaching their target through the gastrointestinal tract can be metabolized in the anaerobic conditions of the lower colon prior to absorption. Bioavailability via various routes of exposure may also vary. For example, intestinal absorption results in a first pass effect that may lead to metabolic detoxication or activation by the liver.

The amount of a chemical that has been absorbed and is available for interaction with biologically significant receptors is called the internal dose. Once absorbed, the chemical can undergo metabolism, storage, excretion or transport within the body. The amount transported to an individual organ, tissue or fluid of interest is termed the delivered dose. The delivered dose may be only a small part of the total internal dose. The biologically effective dose, or the amount that actually reaches cells, sites or membranes where adverse effects occur (US NRC, 1990), may only be a part of the delivered dose. Currently, most risk assessments dealing with environmental chemicals (as opposed to pharmaceutical assessments) use dose–response relationships based on potential (administered) dose or internal dose, since the pharmacokinetics necessary to base relationships on the delivered dose or biologically effective doses are not available. This may change in the future, as more becomes known about the pharmacokinetics of environmental chemicals.

Doses are often presented as dose rates, or the amount of a chemical dose (applied or internal) per unit time (e.g., mg/day), for instance, as dose rates on a per-unit-body-weight basis (e.g., mg/kg per day).

The general equation for potential dose for intake processes, e.g., inhalation and ingestion, is simply the integration of the chemical

intake rate (concentration of the chemical in the medium multiplied by the intake rate of the medium, C × IR) over time:

$$D_{pot} = \int_{t_1}^{t_2} C(t)\ IR(t)\ dt \qquad (2)$$

where D_{pot} is potential dose and IR(t) is the ingestion or inhalation rate.

The quantity t_2–t_1, as before, represents the period of time over which exposure is being examined, or the exposure duration (ED). The exposure duration may contain times where the chemical is in contact with the person, and also times when C(t) is zero. Contact time represents the actual time period where the chemical is in contact with the person. For cases such as ingestion, where actual contact with food or water is intermittent, and consequently the actual contact time may be small, the intake rate is usually expressed in terms of a frequency of events (e.g., 8 glasses of water consumed per day) multiplied by the intake per event (e.g., 250 ml of water per glass of water consumed). Intermittent air exposures (e.g., 8 h exposed/day multiplied by one cubic metre of air inhaled/hour) can also be expressed easily using exposure duration rather than contact time. Hereafter, the term exposure duration will be used in the examples below to refer to the term t_2–t_1, since it occurs frequently in exposure assessments and it is often easier to use.

Equation 2 can also be expressed in discrete form as a summation of the doses received during various events i:

$$D_{pot} = \sum_i C_i \cdot IR_i \cdot ED_i \qquad (3)$$

where ED_i is the exposure duration for event i. If C and IR are nearly constant (which is a good approximation if the contact time is very short), equation 4-3 becomes:

$$D_{pot} = \bar{C} \cdot \bar{IR} \cdot ED \qquad (4)$$

where ED is the sum of the exposure durations for all events, and $\bar{C}$ and $\bar{IR}$ are the average values for these parameters. Equation 4 will not necessarily hold in cases where C and IR vary considerably. In those cases, equation 3 can be used if the exposure can be broken

out into segments where C and IR are approximately constant. If even this condition cannot be met, equation 2 may be used.

For risk assessments, estimates of dose should be expressed in a manner that can be compared with available dose–response data. Frequently, dose–response relationships are based on potential dose (called administered dose in animal studies), although dose–response relationships are sometimes based on internal dose.

Doses may be expressed in several different ways. Solving equations 2, 3 or 4 for example, gives a total dose accumulated over the time in question. The dose per unit time is the dose rate, which has units of mass/time (e.g., mg/day). Because intake and uptake can vary, dose rate is not necessarily constant. An average dose rate over a period of time is a useful number for many risk assessments.

Exposure assessments take into account the time scale related to the biological response studied, unless the assessment is intended to provide data on the range of biological responses (US NRC, 1990). For developmental toxicity effects, a single short-term exposure can cause the adverse health effects. For many non-cancer effects, risk assessments consider the period of time over which the exposure occurred, and often, if there are no excursions in exposure that would lead to acute effects, average exposures or doses over the period of exposure are sufficient for the assessment. These averages are often in the form of average daily doses (ADDs) expressed, for example, in mg/kg body weight per day.

An ADD can be calculated from equation 2 by averaging D_{pot} over body weight and an averaging time, provided the dosing pattern is known so that the integral can be solved. It is unusual to have such data for human exposure and intake over extended periods of time, so some simplifying assumptions are commonly used. Using equation 4 instead of 2 or 3 involves making steady-state assumptions about C and IR, but this makes the equation for ADD easier to solve. For intake processes, then, using equation 4, this becomes:

$$ADD_{pot} = [\,\bar{C} \cdot \bar{IR} \cdot ED] \;/\; [BW \cdot AT] \qquad (5)$$

where ADD_{pot} is the average daily potential dose, BW is body weight, and AT is the time period over which the dose is averaged (converted

to days). As with equation 4, the exposure concentration $\bar{C}$ is best expressed as an estimate of the arithmetic mean regardless of the distribution of the data. Again, using average values for C and IR in equation 5 assumes that C and IR are approximately constant.

For effects such as cancer, where the biological response is usually described in terms of lifetime probabilities, even though exposure does not occur over the entire lifetime, doses are often presented as lifetime average daily doses (LADDs). The LADD takes the form of equation 6, with lifetime (LT) replacing the averaging time (AT):

$$ADD_{pot} = [\bar{C} \cdot \bar{IR} \cdot ED] \ / \ [BW \cdot LT] \qquad (6)$$

5.3 Approaches to quantification of exposure

Exposure (or dose) is assessed generally by one of the following approaches:

a) The exposure can be measured at the point of contact (the outer boundary of the body) while it is taking place, measuring both exposure concentration and time of contact and integrating them (point-of-contact or personal measurement);

b) The exposure can be estimated by separately evaluating the exposure concentration and the time of contact, then combining this information (scenario evaluation);

c) The exposure can be estimated from dose, which in turn can be reconstructed through internal indicators (biomarkers, body burden, excretion levels, etc.) after the exposure has taken place (reconstruction).

These three approaches to quantification of exposure (or dose) are independent, as each is based on different data. This offers the opportunity of checking the accuracy of exposure estimated by one approach through use of an independent approach, where data permit. The independence of the three methods is a useful concept in verifying or validating results. Each of the three has strengths and weaknesses; using them in combination can considerably strengthen the credibility of an exposure or risk assessment.

5.3.1 Measurement at point of contact (personal monitoring)

Point-of-contact exposure measurement evaluates the exposure as it occurs, by measuring the chemical concentrations at the interface between the person and the environment as a function of time, resulting in an exposure profile. The best known example of the point-of-contact measurement is the radiation dosimeter. This small badge-like device measures exposure to radiation as it occurs and provides an integrated estimate of exposure for the period of time over which the measurement has been taken. Another example is the Total Exposure Assessment Methodology (TEAM) studies (US EPA, 1987a) conducted by the EPA and similar multimedia exposure studies in Canada (Otson et al., 1996). In the TEAM studies, a small pump with a collector and absorbent was attached to a person's clothing to measure his or her exposure to airborne solvents or other pollutants as it occurred. A third example is the carbon monoxide (CO) point-of-contact measurement studies where subjects carried a small CO measuring device for several days (US EPA, 1984). Dermal patch studies and duplicate meal studies are also point-of-contact measurement studies. In all of these examples, the measurements are taken at the interface between the person and the environment while exposure is occurring. Use of these data for estimating exposures or doses for periods that differ from those for which the data are collected (e.g., for estimates of lifetime exposures) will require some assumptions.

The strength of this method is that it measures exposure directly, and providing that the measurement devices are accurate, is likely to give the most accurate exposure value for the period of time over which the measurement was taken. It is often expensive, however, and measurement devices and techniques do not currently exist for all chemicals. This method may also require assumptions to be made concerning the relationship between short-term sampling and long-term exposures, if appropriate. This method is also not source-specific, a limitation when particular sources will need to be addressed by risk managers.

5.3.2 Scenario evaluation method (time activity and monitoring/ modelling)

In exposure scenario evaluation, the assessor attempts to determine the concentrations of chemicals in a medium or location and link this information with the time and ways that individuals or populations come into contact with the chemical. The set of

assumptions about how this contact takes place is an exposure scenario.

The first step in a scenario evaluation is usually to characterize the contaminant concentration in the media of concern at the point where contact occurs. This is typically accomplished indirectly by measuring, modelling or using existing data on concentrations in the bulk media, rather than at the true point of contact. An example of a scenario evaluation is presented in Table 1. Since the concentration in the bulk medium is not the same as the exposure concentration, this is a clear source of potential error in the exposure estimate. Generally, the closer the medium can be measured to the point of contact (in both space and time), the less uncertainty there is in the characterization of exposure concentration. Where monitoring data are inadequate, fate models are typically used to estimate chemical concentrations. These models can span a wide range of complexity in terms of spatial dimensions and temporal assumptions (i.e. steady-state versus non-steady-state). Types of fate models include:

- simple dilution models where a measured concentration in an effluent is divided by a dilution factor or the chemical release rate is divided by the bulk flow rate of the medium;

- equilibrium models which predict the distribution of a chemical in the environment based on partitioning ratios or fugacity (the escaping tendency of a chemical from one environmental phase to another);

- dispersion models which predict reductions in concentrations from point sources based on assumed mathematical functions or dispersion properties of the chemical;

- transport models which predict concentration changes over distance and can represent dispersion, biochemical degradation and absorption.

Compilations of existing environmental fate models have been published (OECD, 1989, 1991a; Braat et al., 1991; ECETOC, 1992, 1993; RIVM, 1994). The US EPA has produced a software system called the Integrated Model Evaluation System (IMES) to help assessors select the fate model best suited to their needs (US EPA, 1992). The software prompts users to answer a variety of questions

about their needs and then lists the models that have matching features. The system has information on over 150 models representing all media (air, surface water and groundwater). Model information includes descriptions of the model type, computer requirements, validation testing and contact for obtaining a copy. The Netherlands National Environmental Policy Plan Uniform System for the Evaluation of Substances (USES) is a decision-support system for the rapid quantitative assessment of the hazards and risks of chemicals, including new substances, agricultural pesticides and biocides (RIVM, 1994). USES has been the basis for the development of the European Union System for the Evaluation of Substances (EUSES).

The reliability of modelled estimates of chemical concentration in the general environment depends on how well the model assumptions match reality (i.e. how realistic are the assumptions such as steady-state conditions and homogenous media properties), whether the model performance has been demonstrated under conditions similar to those of concern; and the quantity and quality of input data. Modelling efforts which use input values derived primarily on the basis of default assumptions are generally most useful for screening purposes to highlight areas in which specific additional data are required to estimate exposure more accurately. Further discussion about model uncertainty can be found below.

The next steps involve identifying who is exposed and developing estimates of the frequency and duration of exposure. Like chemical concentration characterization, this is usually done indirectly by use of demographic data, survey statistics, behaviour observation, activity diaries, activity models or, in the absence of more substantive information, assumptions about behaviour. When estimating potential dose, this step also involves estimating how much contact occurs. Table 2 shows examples of standardized reference values for body weights, fluid intake and respiratory volumes. This type of data is also summarized in the Exposure Factors Handbook (US EPA, 1997). This Handbook includes information on consumption rates for various food types, fish ingestion, soil ingestion, dermal contact with soils, body surface area, lifetime, body weight, inhalation rate, breast milk ingestion rate, and activity patterns (time spent swimming, bathing time, time indoors/outdoors, time in vehicles, etc.). For each factor, descriptions are provided of the average values and the variability in the general population. Values are recommended for each factor, with a qualitative indication of the supporting weight of evidence.

Table 1. Estimated daily intake of inorganic fluoride (µg/kg body weight per day), according to age group, by the general population of Canada (from Liteplo et al., 1994)

Route of exposure	0–6 months[a]	7 months–4 years[b]	5–11 years[c]	12–19 years[d]	20 + years[e]
Ambient air[f]	0.01	0.01	0.01	0.01	0.01
Food[g]	14–92	22	16	13	30
Breast milk[h]	0.5–1.1	–	–	–	–
Soil[i]	0.03–1.6	0.02–1.2	0.01–0.4	0.002–0.1	0.002–0.1
"Fluoridated" drinking-water[j]	–	45–77	24–42	17–29	16–27
"Non-fluoridated" drinking-water[k]	–	3.1–12.9	1.7–7.0	1.1–4.8	1.1–4.5
Household products[l]	–	20–60	8.2–20	2.5	1.1
Total intake of breast-fed infants	0.5–2.6	–	–	–	–
Total intake of formula-fed infants	14–94	–	–	–	–
Total intake ("Fluoridated" water)[m]	–	87–160	49–79	33–45	47–58
Total intake ("Non-fluoridated" water)[n]	–	45–96	26–44	17–21	32–36

[a] Assumed to weigh 7 kg, breathe 2 m^3 air, drink 750 ml of breast milk or infant formula (as food), and consume 35 mg soil per day.
[b] Assumed to weigh 13 kg, breathe 5 m^3 air, drink 0.8 litres of water, and consume 50 mg soil per day.
[c] Assumed to weigh 27 kg, breathe 12 m^3 air, drink 0.9 litres of water, and consume 35 mg soil per day.
[d] Assumed to weigh 57 kg, breathe 21 m^3 air, drink 1.3 litres of water, and consume 20 mg soil per day.
[e] Assumed to weigh 70 kg, breathe 23 m^3 air, drink 1.5 litres of water, and consume 20 mg soil per day.
[f] Based on the mean concentration of inorganic (gaseous and particulate) fluoride in ambient air of 0.03 µg/m^3, reported for Toronto, Ontario, and assuming the concentration in indoor air is identical to (outdoor) ambient air.

Table 1 (contd).

[g] Formula-fed infants (0–6 months): based on the mean concentrations of inorganic fluoride in infant formulas purchased in the USA of 0.127 and 0.854 mg/litre reported for ready-to-use, milk-based formula and soy-based powdered formula (prepared with drinking-water containing 1 ppm fluoride), respectively, and assuming infants are exclusively formula-fed and consume 750 ml formula per day. General population (7 months and older): based on levels of inorganic fluoride detected in 109 individual foods from Canada (and the USA), in the following food groups: 0.01–0.80 µg/g in dairy products, 0.12–1.02 µg/g in cereal products, 0.01–0.58 µg/g in fruit, 0.01–0.68 µg/g in vegetables, 0.04–4.57 µg/g in meat/fish/eggs; 0.05–0.13 µg/g in fats, 0.11–0.35 µg/g in nuts/legumes, 0.02–0.86 µg/g in foods containing primarily sugar, 0.41 –0.84 µg/g in soup, 4.97 µg/g in tea; and the daily intake of each food item by the various age groups of the general population of Canada.

[h] Based on the mean concentrations of inorganic fluoride of 4.4 and 9.8 ng/g reported for samples of breast milk from mothers living in communities served by "non-fluoridated" and "fluoridated" drinking-water, respectively, assuming the density of breast milk is equal to 1.0 g/ml.

[i] Based on a range of concentrations of total inorganic fluoride of 6 µg/g reported by Sidhu (1982) for soil collected in Newfoundland, to 309 µg/g [mean concentration in Canadian surface soil (0–130 cm depth)].

[j] Based on a range of mean concentrations of inorganic fluoride in "fluoridated" drinking-water of 0.73 mg/litre, determined from fluoride levels in 3 communities in Newfoundland and Labrador, to 1.25 mg/litre, determined from 2 communities in the Yukon. "Fluoridated" refers to drinking-water to which inorganic fluoride has been intentionally added for the prevention of dental caries.

[k] Based on a range of mean concentrations of inorganic fluoride in "non-fluoridated" drinking-water of (at least) 0.05 mg/litre (reported for 3 communities in British Columbia), to 0.21 mg/litre (reported for an unspecified number of communities in the Yukon). "Non-fluoridated" refers to drinking-water to which inorganic fluoride has not been intentionally added for the prevention of dental caries.

[l] Based on a mean concentration of inorganic fluoride in most dentifrice products of 1000 µg/g and an estimated intake of dentifrice of 0.26–0.78 g/day for children 7 months to 4 years of age, 0.22–0.54 g/day for children 5 to 11 years of age, 0.14 g/day for adolescents 12 to 19 years of age, and 0.08 g/day for adults 20 + years of age, assuming an average of 2 brushings per day.

[m] Estimated total daily intake of inorganic fluoride by individuals consuming "fluoridated" drinking-water in Canada.

[n] Estimated total daily intake of inorganic fluoride by individuals in Canada consuming drinking-water that is not "fluoridated".

Table 2. Human contact parameters (from ICRP, 1974)

Body weight, kg

Adult male	=	70
Adult female	=	58
Average	=	64[a]

Daily fluid intake (milk, tap water, other beverages), ml/day

Normal conditions:		
Adults	=	1000–2400, representative figure = 1900[b]
Adult male	=	1950
Adult female	=	1400
Child (10 years)	=	1400
High average temperature (32 °C):		
Adults	=	2840–3410
moderate activity:		
Adults	=	3700

Respiratory volumes

8-h respiratory volumes, litres per 8 h resting:

	Adult man	=	3600
	Adult woman	=	2900
	Child (10 years)	=	2300
light/non-occupational activity:	Adult man	=	9600
	Adult woman	=	9100
	Child (10 years)	=	6240

Daily inhalation volume, m^3 (8 h resting, 16 h light/non-occupational activity)

Adult male	=	23
Adult female	=	21
Average adult	=	22
Child (10 years)	=	15

[a] WHO uses 60 kg for calculation of acceptable daily intakes and water quality guidelines (IPCS, 1987b; WHO, 1993).

[b] WHO uses a daily per capita drinking-water consumption of 2 litres in calculating water quality guidelines (WHO, 1993).

The chemical concentration and population characterizations are ultimately combined in an exposure scenario, and there are various ways to accomplish this. One of the major problems with this approach is that the limiting assumptions or boundary conditions (e.g., steady-state assumptions) do not always hold true. Two ways to address to

this aspect are: (a) to evaluate the exposure or dose equation under conditions where the limiting assumptions do hold true; or (b) to deal with the uncertainty caused by the divergence from the boundary conditions. As an example of the first option, in the microenvironment method, utilized primarily for evaluating airborne exposures in the general environment but including contact with the skin in the occupational environment, segments of time and location are evaluated where the assumption of constant concentration is approximately true and then summed over all such time segments for a total exposure for the respiratory route, effectively removing some of the boundary conditions. While estimates of exposure concentration and time-of-contact are still derived indirectly by this method, the concentration and time-of-contact estimates can be measured for each micro-environment. This avoids much of the error due to using average values in cases where concentration varies widely along with time-of-contact.

As examples of the second approach, there are various tools used to describe uncertainty caused by parameter variation, such as Monte Carlo analysis (see below).

One strength of the scenario evaluation approach is that it is usually the least expensive method of the three. In addition, it is particularly suited to analysis of the risk consequences of proposed actions. It is both a strength and a weakness of scenario development that the evaluation can be performed with little or no data; it is a technique that is best used when some knowledge exists about the soundness, validity and uncertainty of the underlying assumptions.

5.3.3 *Biomarkers of exposure/estimation of internal dose*

Exposure can also be estimated after it has taken place. If a total dose is known, or can be reconstructed, and information about intake and uptake rates is available, an average past exposure rate can be estimated. Reconstruction of dose relies on measuring internal body indicators after exposure, intake and uptake have already occurred, and using these measurements to back-calculate dose. However, the data on body burden levels or biomarkers cannot be used directly unless a relationship can be established between these levels or biomarker indications and internal dose, and interfering reactions (e.g., metabolism of unrelated chemicals) can be accounted for or ruled out. Biological tissue or fluid measurements that reveal the presence of a

chemical may indicate directly that an exposure has occurred, provided the chemical is not a metabolite of other chemicals. These biomarkers of exposure are necessarily limited, however, to ethical relatively non-invasive techniques.

Biological monitoring can be used to evaluate the amount of a chemical in the body by measuring one or more of the following items (not all of these can be measured for every chemical):

- the concentration of the chemical itself in biological tissues or sera (blood, urine, breath, hair, adipose tissue, etc.);
- the concentration of the chemical's metabolite(s);
- the biological effect that occurs as a result of human exposure to the chemical (e.g., alkylated haemoglobin or changes in enzyme induction);
- the amount of a chemical or its metabolites bound to target molecules.

Biomarkers can be used to estimate chemical uptake during a specific interval if background levels do not mask the marker and the relationships between uptake and the marker selected are known. The time of sampling for biomarkers can be critical. Establishing a correlation between exposure and the measurement of the marker, including pharmacokinetics, can help optimize the sampling conditions.

The strengths of this method are that it demonstrates that exposure to and absorption of the chemical has actually taken place, and it theoretically can give a good indication of past exposure. Biomarkers integrate exposure from all sources and take into account absorption, which may vary considerably due to a variety of factors including environmental characteristics, genetic predisposition, age, gender, ethnicity and/or lifestyle factors.

For many environmental pollutants, the flow of events between exposure and health effects is not well understood. Biomarkers help address this problem by improving the sensitivity, specificity and predictive value of detection and quantification of adverse effects at low dose and early exposure (ECETOC, 1989; Fowle, 1989; Fowle &

Sexton, 1992; US NRC, 1992). Sensitive subpopulations can be better pinpointed by biomarkers that measure increased absorption rate or a more severe biological response to a given environmental exposure (Lauwerys, 1984; ECETOC, 1989; Fowle & Sexton, 1992; Hemminki, 1992; US NRC, 1992).

Over the last decade, biomarker methods have been developed for the detection of exposure to carcinogens and other DNA-damaging agents. These methods involve the detection of the parent compound or metabolites in body fluids or adducts bound to DNA or protein, such as haemoglobin and albumin (Shuker, 1989; Wogan, 1989, 1992; Beland & Poirier, 1993). Methods for detecting exposure to DNA-damaging agents are classifiable into two categories: a) measurements of levels of genotoxic chemicals, their metabolites and/or derivatives in cells, tissues, body fluids or excreta; and b) measurements of biological responses such as cytogenetic changes in exposed individuals.

Biomarker methods have also been developed to detect exposure from tobacco use (polycyclic aromatic hydrocarbons (PAHs), aromatic amines and specific nitrosamines), dietary exposure (aflatoxins, *N*-nitrosamines, heterocyclic amines), medicinal exposure (cisplatin, alkylating agents, 8-methoxypsoralen, ultraviolet photoproducts), occupational exposure (benzene, ethylene oxide, styrene oxide, vinyl chloride, aromatic amines, PAHs) and oxidative damage (8-hydroxyguanine) (Perera, 1987, 1988; Groopman et al., 1988; Wogan, 1989, 1992; Hemminki et al., 1990; Skipper & Tannenbaum, 1990; Beland & Poirier, 1993).

The drawbacks of the reconstructive method are that it will not work for every chemical, due to interferences or the reactive nature of the chemical, it has not been methodologically established for very many chemicals, data relating internal dose to exposure are needed, and it may be expensive.

5.4 Variability and uncertainty

Characterization of variability and uncertainty is an integral component of all steps in risk assessment. However, quantitative characterization of these aspects is best developed for exposure estimation. Variability (the receipt of different levels of exposure by different individuals) is generally distinguished from uncertainty (the

lack of knowledge about the correct value for a specific exposure measure or estimate). Most of the exposure and risk descriptors deal with variability directly, but, wherever possible, estimates of the uncertainty of these descriptors are included. This may be done qualitatively or quantitatively, and it is beyond the scope of this report to discuss the mechanics of uncertainty analysis in detail.

Not all approaches historically used to construct measures or estimates of exposure attempted to distinguish variability and uncertainty. In particular, in many cases in which estimates were termed worst case, focusing on the high end of the exposed population and also selection of high-end values for uncertain physical quantities resulted in values that were seen to be quite conservative. By using both the high-end individuals (variability) and upper confidence bounds on data or physical parameters (uncertainty), these estimates might be interpreted as "not exceeding an upper bound on exposures received by certain high-end individuals".

Variability in exposure occurs when some members of the population are exposed more than others. For example, exposures via one or more routes to some substances may be elevated for persons living in the vicinity of point sources (such as industrial emissions), depending on the form in which these substances are released and their subsequent environmental transport and transformation. The intake of some substances by subsistence hunters or fishermen may also be elevated due to accumulation in the game species that they consume. Owing to the variation in exposure patterns at various stages over a lifetime, exposure is often estimated for various age groups of the general population; for example, Health Canada (1994) estimates intake for several defined periods of life: for infants (0–6 months), pre-school children (7 months to 4 years), elementary school children (5–11 years), teenagers (12–19 years), and adults (20 years of age and older). Hence, the period up to 6 months of age is when many infants may be exposed to substances present in breast milk. In addition, pre-schoolers' exposure to contaminants in soil may be significantly higher than that for other age groups. Children of all ages have relatively high intakes of food per unit of body weight. Adulthood is a period of long-term lower-level exposure via most environmental media, with relatively high potential exposure to some substances through activities such as the use of consumer products. An example of age-stratified estimates of exposure is presented in Table 1, showing fluoride exposure for five age groups in the general population.

5.4.1 Assessing uncertainty

Assessing uncertainty may involve simple or very sophisticated techniques, depending on the requirements of the assessment. "Uncertainty characterization" generally involves a qualitative discussion of the thought processes that lead to the selection and rejection of specific data, estimates, scenarios, etc. For simple exposure assessments, where not much quantitative information is available, uncertainty characterization may be all that is necessary.

"Uncertainty assessment" is more quantitative and can include simpler measures (i.e. ranges) and analytical techniques (i.e. sensitivity analysis) or, to the extent needed to support the decision for which the exposure assessment is conducted, more complex measures and techniques.

Uncertainty in exposure assessment can be classified into three broad categories:

1. Uncertainty regarding missing or incomplete information needed to fully define the exposure and dose (scenario uncertainty).

2. Uncertainty regarding some parameter (parameter uncertainty).

3. Uncertainty regarding gaps in scientific theory required to make predictions on the basis of causal inferences (model uncertainty).

Identification of the sources of uncertainty in an exposure assessment is the first step toward eventually determining the type of action necessary to reduce that uncertainty.

5.5 Exposure settings

Human exposure occurs in the general environment, at occupational settings or in households/businesses or other areas where consumer products are used. Each of these settings is discussed below.

5.5.1 Exposure in the general environment

Exposure to environmental substances may occur by inhalation, ingestion and/or dermal absorption from air, water, food and soil. Estimation of the total daily intake (often expressed as μg/kg body

weight/day) from all sources is critical in assessing the true magnitude of risk associated with indirect exposure to substances in the general environment. This is often referred to as a "multimedia" approach (Table 1).

The US EPA has sponsored the development of a computer software programme called Risk Assistant for conducting site-specific risk assessments for environmental chemicals. The programme prompts the user to identify the chemicals of concern, the contaminated media and concentrations in those media. The programme automatically lists the possible pathways of exposure associated with the contaminated media. The user can select which of these pathways is of interest. The user can choose to use default assumptions for exposure parameters or modify them as desired.

5.5.2 Occupational settings

Workers are exposed in the occupational environment by inhalation, through dermal contact or by ingestion, although the latter is not often quantified. Dermal and inhalation monitoring as well as biological monitoring (biomarkers) are often required to characterize adequately the exposure of special subgroups of workers such as mixers, loaders and applicators or pesticides (e.g., farm families) (WHO, 1986; US EPA, 1987b; Curry & Iyengar, 1992).

Exposure by inhalation in the occupational environment is often expressed as the concentration of a substance in the breathing zone averaged over a reference period. This reference period is often 8 h to represent long-term exposure or 15 min for short-term exposure. Exposure to the skin is generally expressed as potential dose rate predominantly to the hands and forearms and is often available only as output of models.

Measured data on concentrations of chemical substances in the occupational environment are often available from routine industrial hygiene or dedicated surveys. The suitability of the use of such information in estimation of exposure must be carefully assessed based on consideration of factors such as representation of levels, time periods and processes.

Cumulative exposure (average intensity multiplied by time) is one of the most common summary measures for exposure in epidemio-

logical studies of occupationally exposed populations. However, there may also be intermittent peak exposures that could be of importance but difficult to integrate properly in a single concentration–time exposure model (Ulfvarson, 1992). The elimination rate of a pollutant is of particular importance in considering the possible impact of peak versus continuous exposure (Axelson & Westberg, 1992).

Where monitoring data are incomplete or not available, occupational exposures can also be modelled (EC, 1996), primarily to highlight areas in which specific additional data are required to estimate exposure more accurately. To date, these models are restricted primarily to prediction of mean concentrations over extended averaging periods (e.g., 8 h). For example, for workplace exposure modelling in the European Union, criteria to describe broadly the types of exposure possible address the physical properties of process chemicals, their use pattern and pattern of control. Descriptors for the physical properties of process chemicals include, for example, gas, liquid of high vapour pressure, liquid of medium vapour pressure, solid respirable dust, solid, granular or aerosol. Descriptors of use patterns include closed system, within a matrix or wide dispersive. Descriptors of control patterns include full containment, local exhaust ventilation, etc. Combinations of various subsets of these descriptors result in 160 complementary fields to which numerical ranges of concentrations have been assigned based on measured data in the United Kingdom National Exposure Database.

Dermal exposure in occupational settings most commonly involves hands and forearms (approximately 2000 cm^2) (EC, 1996). Dermal exposure to gases and vapours is typically assumed to be very low. The EU classifies the potential for dermal exposure as none, incidental (approximately one event per day), intermittent (2 to 10 events per day) or extensive (>10 events per day). Exposure ranges are estimated based on several databases and the published literature. Criteria for both inhalation and dermal exposure are incorporated within a knowledge-based electronic system (EC, 1996).

5.5.3 *Consumer products*

A consumer product is one which can be purchased from retail outlets by members of the general public. People of any age, either sex, and in any stage of health may be exposed to chemicals in these products. Much of the discussion below is based on an EU document

providing guidance on assessing exposure to chemicals in consumer products (EC, 1996).

Exposure to chemicals in consumer products is often considered as single events, a series of repeated events or as continuous exposure (e.g., concentrations in indoor air resulting from storage and use of such products). Routes of exposure are dermal (e.g., cleaning agents, cosmetics, shampoos), inhalation (e.g., hair spray, powdered detergents) or by ingestion (e.g., food, drinks or swallowing of tooth paste; see Table 1 for an example of the latter).

The assessment of the exposure to consumer products can be conducted following an iterative procedure, which starts with an initial "screening". This screening would identify if a substance is used as or in consumer products where further consideration and possibly quantification of exposure is necessary.

If a substance is used in more than one consumer product, or if more than one mode of use is employed (e.g., painting and spraying), or if the product could reasonably be expected to be used in other ways (e.g., use of a washing machine detergent for washing by hand), it may be necessary to assess exposure for each case. In addition, if the substance is used in different consumer products or has different modes of use, the exposure assessment could examine those uses for which the highest exposure is expected to occur on a regular basis. The cumulative exposure expected from the use of the same substance in different products may also be considered.

To assess the exposure to substances present in consumer products, information is needed on two sets of parameters: contact parameters and concentration parameters. The contact parameters denote where, how long and how often contact with the consumer occurs. The concentration parameters are needed to estimate the concentration of a substance in a medium that might come into contact with the body. This is not necessarily equal to the concentration of the substance in the product, because a product might be diluted, mixed, undergo evaporation, etc., before the substance of interest actually reaches the human body.

By combining the contact parameters with the concentration estimates, exposure or dose can be estimated. As discussed in section 5.2, exposure and dose can be estimated in a variety of ways. Exposure

to contaminants in air is commonly estimated in concentration–time units, as shown in equation 1. Exposure to ingested contaminants is commonly estimated as a potential dose, as shown in equation 2. Dermal exposures are commonly estimated as an internal dose.

For example, exposure to a component of a hair spray used twice a day, could be based on assumptions that the weight of product used per event is 5000 mg, the weight fraction of the chemical substance is 1%, the inhaled fraction is 70%, the room volume is 2 m^3, the volume inhaled is 0.8m^3, and the exposure time is 6 min (EC, 1996). Dermal exposure to a component of a watch strap could be estimated taking into consideration the area of contact, the thickness and density of the material, the weight fraction of the chemical substance, period of contact per day and fraction likely to migrate from strap to skin, and fraction or rate that the chemical is absorbed into the body.

For a realistic assessment, the following data would ideally be available:

a) Contact data

- frequency of product use
- duration of product use per event
- site of product use, including size of room
- air exchange rate

b) Concentration data

- weight fraction of substance in the product
- if available, concentration of substance in the products as used, e.g., after dilution or evaporation has occurred

c) Product use

- physical form of product (aerosol, dry powder, large crystals, liquid, gas, etc)
- amount of product used per event
- contact surface (if appropriate)
- intended use of product

The diversity of consumer products does not allow for a single set of information sources, handbooks or databases to be consulted.

Rather, it is necessary to explore which information sources apply to the substance of interest. Below, an overview is provided of possible information sources that may be useful.

i) Product registers are available in some countries and may provide information on whether the substance under consideration is present in marketed consumer products.

ii) Specific information on use durations and contact frequencies for consumer products is often lacking. An estimate of these parameters can be derived from time budget data where available. Time budgets comprise information on the behaviour of a population during a day, week or year. Because time budgets may vary geographically, it is useful to check if the national statistical agencies have gathered such data on a regional basis.

iii) Information on actual product use by the consumer is not widely available. The directions of the manufacturer provide information on the recommended use, not on the way products may be handled before or after actual use nor on reasonably foreseeable misuse. Although information can be gained from Poison Control Centres and case studies reported in the literature, such data generally represent the more extreme misuses of the product and might not be very informative about the normal range of uses.

iv) Information accompanying exposure assessment computer programmes (see below) may also be useful sources of data.

v) Some countries require manufacturers of certain products (e.g., cosmetics, toys, pharmaceuticals, food contact materials, pesticides) to provide data useful for estimating exposure. Assessors should use these data, where available and appropriate, when conducting the exposure assessment.

Measured data useful for exposure assessment may be available for a number of substances (e.g., concentrations of solvents in room air as a consequence of the application of consumer products containing a solvent or of their migration from articles; concentration of polymer softeners or other additives migrating from food contact materials, children's toys or other articles).

The reliability and representativeness of the measured exposure data may be evaluated considering:

- if they represent the whole group of consumers or a certain subset;
- if they reflect all exposure scenarios of concern;
- if they describe the foreseeable use;
- if they reflect the complete range of reasonable exposure values or only an isolated value in any part of this range.

The European Union (EC, 1996) has presented a variety of simple algorithms that can be used to assess consumer exposure for a number of common exposure scenarios. Many give an exposure value per event (single use), but are readily adaptable to different situations. In addition, the European Union (EC, 1996) has summarized a variety of more complex computer models for assessing consumer exposure (CONSEXPO, THERdbASE, US EPA household exposure models MCCEM and HOUSE EXP: SCIES, DERMAL, FLUSH and AMEM).

6. RISK CHARACTERIZATION AND IMPLICATIONS FOR RISK MANAGEMENT

6.1 General considerations

The traditional goal of regulating risks is to protect and improve public health and well-being. Since 1980, risk assessment has increasingly formed the methodological basis in many countries, particularly industrialized nations, for the regulation of chemicals in the occupational and general environments.

Risk assessment, comprising the elements of hazard identification, dose–response assessment, exposure assessment and risk characterization, is now recognized as an essential tool by many national, regional and international bodies, and it is also recognized that it is a continuously evolving process which has changed considerably in the last two decades (US NAS, 1983; Somers, 1987,1993; UK HSE, 1989; Scala; 1991; Ballantyne et al., 1993; EC, 1996). It should be recognized as a vital mechanism for the delivery of salient information to decision-makers.

Risk characterization aims to provide a synthesis of estimates of exposure levels and health risks; it also summarizes sources of uncertainty in scientific data and provides the primary basis for making risk management decisions. The results of a risk assessment (as summarized in the characterization) are the basis of identification of chemical exposures that pose no significant health threat and those that present significant risks. Additionally, to the extent permitted by available data, risk characterization indicates how risk varies with exposure, to help risk managers evaluate a range of options. It assists risk management officials and decision makers in allocating scarce resources and money to the most important resolvable uncertainties and reduction of risks. However, the results of risk assessment, as summarized in the risk characterization, are but one consideration in health and environmental decision-making.

The term "risk management" encompasses all of those activities required to reach decisions on whether an associated risk requires elimination or necessary reduction. Risk management strategies/or options can be broadly classified as regulatory, non-regulatory, economic, advisory or technological, which are not mutually exclusive. Thus legislative mandates (statutory guidance), political

considerations, socioeconomic values, cost, technical feasibility, populations at risk, duration and magnitude of risk, risk comparison, and possible impact on trade between countries can generally be considered as a broad panoply of elements that can be factored into final policy or rule-making. Key decision factors such as the size of the population, the resources, costs of meeting targets and the scientific quality of risk assessment and subsequent managerial decisions vary enormously from one decision context to another (Stern, 1986; Ricci & Cox, 1987; Somers, 1987, 1993; Environ, 1988; Munro & Morrison, 1990; Merrill, 1991; Scala, 1991; Presidential/ Congressional Commission on Risk Assessment and Risk Management, 1997a,b).

It is also recognized that risk management is a complex multidisciplinary procedure that is seldom codified or uniform, frequently unstructured, but which can respond to evolving input from a wide variety of sources (Stern, 1986). Increasingly, risk perception and risk communication are recognized as important elements that must also be considered for the broadest possible public acceptance of risk-management decisions (Krewski et al., 1987; Slovic, 1987, 1993; Kraus & Slovic, 1988; Konheim, 1988; Cohrssen & Covello, 1989; US NRC, 1989; Pariza, 1992; ILSI/National Safety Council, 1993; Morgan, 1993; Singer & Endreny, 1993; Sandman et al., 1993; Van Eijndhoven et al., 1994).

6.2 Considerations in risk characterization

Definitions and guidance for risk characterization have been published in US EPA (1996b), where it is defined as:

> "a summary, integration, and evaluation of the major scientific evidence, reasoning and conclusions of a risk assessment. It is a concise description of the estimates of potential risk and the strengths and weaknesses of those estimates."

Similarly, the European Union defines risk characterization as: "the estimation of the incidence and severity of the adverse effects likely to occur in a human population or environmental sphere due to actual or predicted exposure to a substance, and may include risk estimation, i.e. the quantification of that likelihood (Hertel, 1996).

A risk characterization is the final step in risk assessment. It is designed to support risk managers by providing, in plain language, the essential scientific evidence and rationale about risk that they need for decision-making. In risk characterization, estimates of the risk to human health under relevant exposure scenarios are provided. Thus, a risk characterization is an evaluation and integration of the available scientific evidence used to estimate the nature, importance and, where possible, the magnitude of human and/or environmental risk, including attendant uncertainty, that can reasonably be estimated to result from exposure to a particular environmental agent under specific circumtances. It is important that risk characterizations be clear, transparent and reasonable.

For the risk manager, a risk characterization answers the question: What is the impact (in terms of potential occurrence of adverse effects or increased risk) from exposure to the agent? Along with the concise description of risk, a characterization addresses the uncertainty in the underlying data and models. The characterization provides a sense of the degree of confidence in the risk estimates and a sense of where the supporting data lie on the continuum between evidence that is based on humans, or is highly relevant to humans, and evidence that is based on animals or *in vitro* experiments.

The following are sample questions of risk managers that are commonly addressed in risk characterization:

1) What is the bottom line of the risk assessment?

2) Does the risk assessment provide sufficient information to support a regulatory decision?

3) What is the range of uncertainty around the estimated exposure level and the projected number of people who may be exposed to the chemical? Do we know if people are actually being exposed to the levels identified in the risk assessment? Are these levels of public health concern?

4) What data gaps are likely to elicit criticism of the risk estimate and/or selected risk management options? There will always be data gaps, but which are the ones that may lead to criticism of the risk assessment or of the risk management options and decision(s)?

5) Are studies being conducted that will "soon" provide new information that could fill a critical data gap or gaps?

6) Has the risk assessment been peer reviewed? If so, by whom, and what was the outcome of the review?

7) Indicate how likely, or if, there is a chance of zero risk. Has zero risk actually been ruled out?

8) What is the key parameter that drives the analysis? Is there research on the horizon that will address this key parameter and reduce its uncertainty? How much interest is there in issues surrounding this parameter?

9) If studies were excluded, what would be the consequence for the risk assessment results? What was the rationale for excluding these studies?

Other questions primarily concern the issue of uncertainty. Data lie on a continuum from strong evidence in humans (based on extensive epidemiology and/or other clinical/field observations) to weak evidence in humans, animals or other test systems (based on incomplete data in one or a limited number of species, or structure–activity relationships). Confidence in the conclusions of the risk assessment and the estimate of risk also lie on a continuum from high to low. This degree of confidence is based, to a large extent, on the completeness, quality and consistency of the database (i.e. the weight of evidence). Where do the results of the risk assessment fit on the continuum from high to low confidence?

- What are the specific conditions of exposure believed to cause or contribute to the risk? Have exposures and/or dose been measured in the population of interest? If so, has it been possible to relate exposure to actual body burden? If exposures have been calculated through analogy, modelling, or other estimation techniques, what evidence is there that the estimates are realistic?

- What is the degree of confidence in the existence of the risk and the magnitude of the risk estimate? If the risk is based on animal models, is there an observable parallel between humans and the positively responding animal species in terms of the absorption, metabolism, distribution and excretion of the chemical of

interest? If not, what is the basis for thinking such a parallel exists? Is there epidemiological evidence indicating that comparable effects seen in the animal model have been seen in human populations (e.g., heavily exposed occupational or environmental settings, accidents)?

- Can population subgroups be identified who are at increased risk of exposure and/or especially sensitive to such exposures? At a given exposure or dose level, are there observable differences in the range of response among different human subgroups (e.g., infants, children, healthy adults, the elderly)? If so, have these differences been evaluated and employed in the models used to calculate specific risks? If not, what evidence provides the basis for conclusions drawn about differences in sensitivity among subpopulations and their (potential) risks?

6.3 Considerations in risk management

Decisions concerning management of risks are made on the basis of identified and quantified risk(s), and the potential for impact on individual humans, groups, populations and the environment. This involves consideration of socioeconomic, political, risk–benefit and cost–benefit factors.

The analytical tools of risk assessment and management, as applied to chemicals with a potential for adverse effects on human health and environmental integrity, have assumed a more critical role in decision-making in many countries and are having an increasing impact on the political process. Potentially many jobs, new products and industrial facilities can be created, threatened or protected by the outcomes of risk assessment and management.

6.3.1 *Societal factors*

The actual level of risk considered "acceptable" must be a societal and political judgement taking into account such factors as benefit of the chemical or process, and the cost of its replacement or removal.

There is increasing concern that a disproportionate share of human health risks, e.g., from environmental pollution, is being incurred by low-income deprived and minority populations in developed and developing countries, and that this has not been

sufficiently addressed in requisite risk evaluations and managerial decisions (Mushak, 1993; Silbergeld, 1993; Zimmerman, 1993). It is important to recognize, however, that lifestyle factors are often more important in determining health status in this regard. The term "environmental equity" has been applied to the perceived unequal burdens borne by minorities and the poor in terms of where municipal landfills, incinerators, hazardous waste sites and industries producing toxic emissions are located. Race and socioeconomic status are also linked in some studies to chronic exposures to greater than acceptable levels of environmental pollution such as lead (Mushak, 1993; Silbergeld, 1993). The term "environmental justice" refers to diverse environmental regulations, environmental law enforcement and environmental clean-up programmes, including those in the workplace. Hence a growing body of scientific evidence and political advocacy is focusing attention on what is increasingly considered in some quarters as the inequitable distribution of risk in society. The concept of environmental justice is being built into national and supranational regulatory policy considerations. Requirements to conduct risk management are increasingly being incorporated into national and supranational legislation e.g., European Commission Regulation CEC No. 1488/94, (EC, 1994).

In contrast, it needs to be recognized that regulations that are too stringent may impact unnecessarily adversely on the socioeconomic and, hence, health status of populations.

6.3.2 *Individual and population risks*

Individual risk can be defined as the probability of someone from a certain group (or sub-group) suffering health effects from exposure to a toxicant during an established period (e.g., a year or lifetime). The distinction made between individual risks for persons from a critical group and that for persons from the whole population is important because the acceptability of a certain individual risk varies according to the size of the group running the risk. An individual risk can be considered when effects are involved for which no threshold value exists (stochastic effects), e.g., carcinogens, or when exposures are involved that are higher than existing threshold values for non-stochastic effects.

Frequently, individual risks are calculated for some or all of the persons in the population being studied and are then put into the

context of where they fall in the distribution of risks for the entire population. Key questions often asked when considering strategies for dealing with individual risk include:

- to what risk levels are the persons at the highest risk subjected?
- can individuals with a high degree of susceptibility be identified?
- what is the average individual risk?
- what is the estimate of the probability that an individual will suffer an adverse effect given a specific set of exposure circumstances?

It has also been suggested that sub-groups of the population could be considered in a meaningful risk management scenario. The different factors predisposing individuals to sensitive responses to pollutants include: developmental processes, existing disease, prior exposure to a particular chemical, chemical class or group of chemicals that can act mechanistically in a similar manner, nutritional deficiencies, and tobacco smoking and alcohol consumption (Seidman et al., 1991; US EPA, 1992).

Group or population risk (which generally is calculated) is defined as the chance that a certain group of individuals in a certain environment will simultaneously experience the detrimental consequences of a significant exposure to a toxicant(s) during a period, e.g., a year or lifetime.

A clear trend has not yet emerged concerning the question as to whether risks to individuals, risks to groups or populations, or both, are to be considered in significant risk decisions (Environ, 1988; Rodricks, 1992; US EPA, 1992). For example, is a large risk to a small number of individuals more important from a public health perspective than a small risk to a large number of people (general public ingesting a food or water contaminant for a considerable time period)? A suggested first step following any risk evaluation could be a determination of whether the risk is large enough to threaten the public health to a significant degree (Environ, 1988). Resources are limited and there will always be the possibility that some fraction of the population will respond adversely to a compound or mixture regardless of the exposure. The ultimate question could be (given the limited resources in every society) what percentage of individuals is society unable to protect in this way? Certain sub-groups, for example idiosyncratic responders, may be given protection by appropriate product labelling and information programmes.

6.3.3 Comparative risk

Risk implies uncertainty and subsequent risk evaluations and risk management decisions are concerned with the concept of probability. There is an apparent lack of consensus concerning the appropriate background risk with which to make comparisons (Environ, 1988; US NRC, 1989). While many analysts would find it difficult to compare voluntary assumed risks to involuntarily assumed risks, proponents of risk comparisons strongly suggest that there should be consolidation and greater efforts by those engaged in risk evaluation to identify, assess and compare risks to public health and the environment posed by the highest risk hazards (Wilson & Crouch, 1987; Wiener, 1993). Comparisons should be seen as only one of a number of inputs to risk decisions, not as a primary determinant (US NRC, 1989).

However, it is also suggested that many people do not perceive the various threats to health and well-being simply as matters of probability (Slovic, 1987; Kraus & Slovic, 1988; Pariza, 1992; Sandman et al., 1993). Indeed, estimated risks of death or disease associated with exposure to chemicals in the general environment are often similar to those considered rare, such as being struck by lightening or dying in an airplane crash, although they are not perceived as such (Wilson, 1990). Moreover, people tend not to be deeply concerned about risks that are a matter of choice such as smoking or motorcycle riding. However, they do expect that governments pay attention to risks that they cannot control, even though these might be considerably less.

6.3.4 Risk perception

Whereas analysts employ risk assessment, risk evaluation and risk management to evaluate hazards and formulate strategies and regulations for their reduction or elimination, the majority of individuals rely on intuitive judgements typically called "risk perception". For these people, the experience with hazards tends to come from the news media, which principally document mishaps and threats occurring globally (Slovic, 1987, 1993; Kraus & Slovic, 1988; Cohrssen & Covello, 1989; Sandman et al., 1993; Van Eijndhoven et al., 1994).

Risk perception is being increasingly recognized as an important factor influencing both risk evaluation and risk management. A major

factor that influences the complexity of the social debate over appropriate laws and regulations is the nature and extent of the perceived threat to health. The message that is frequently conveyed to the public is that government standards for risk assessment, risk evaluation and regulatory action are inconsistently applied, subject to bureaucratic manipulation, and subject to alteration depending on the degree of economic impact on the affected industry (Munro & Morrison, 1990).

Different people perceive risks differently, depending on the likelihood of adverse effects, whom it affects, how familiar, widespread and dreaded the effects are, how a hazard affects individuals personally, and whether or not individuals have voluntarily agreed to bear the risks. Perceptions of risk are also influenced to a large degree by the supposed benefits derived from accepting the risk (Slovic, 1987; Krewski, et al., 1987; Kraus & Slovic, 1988; Cohrssen & Covello, 1989; Pariza, 1992; Morgan, 1993; Sandman et al., 1993).

Risks perceived as potentially uncontrollable, capable of causing a catastrophe on a global scale or risking future generations cause public anxiety. Fig. 3 illustrates a mosaic of public perception of risks in terms of risk space quadrants; the upper right quadrant of this space captures uncontrollable risks that are most likely to provoke calls for government regulation (Morgan, 1993).

Tables 3 and 4 further depict qualitative factors affecting risk perception (US NRC, 1989; Scala, 1991). While different people weigh these factors differently in reaching their overall perceptions of the riskiness of a hazard, the set of factors that are important in determining relative perceptions of risk go well beyond the statistical frequency, magnitude and uncertainty of effects. Public opinion on acceptable risk constantly changes, usually in the direction of further risk reduction, which provides further impetus for additional legislation and regulation in many quarters (Munro & Morrison, 1990).

6.3.5 Risk and hazard communication

Implicit in the process of risk evaluation and management is the increasingly recognized role of communication (Cohrssen & Covello, 1989; US NRC, 1989; Morgan, 1993; Sandman et al., 1993; Slovic,

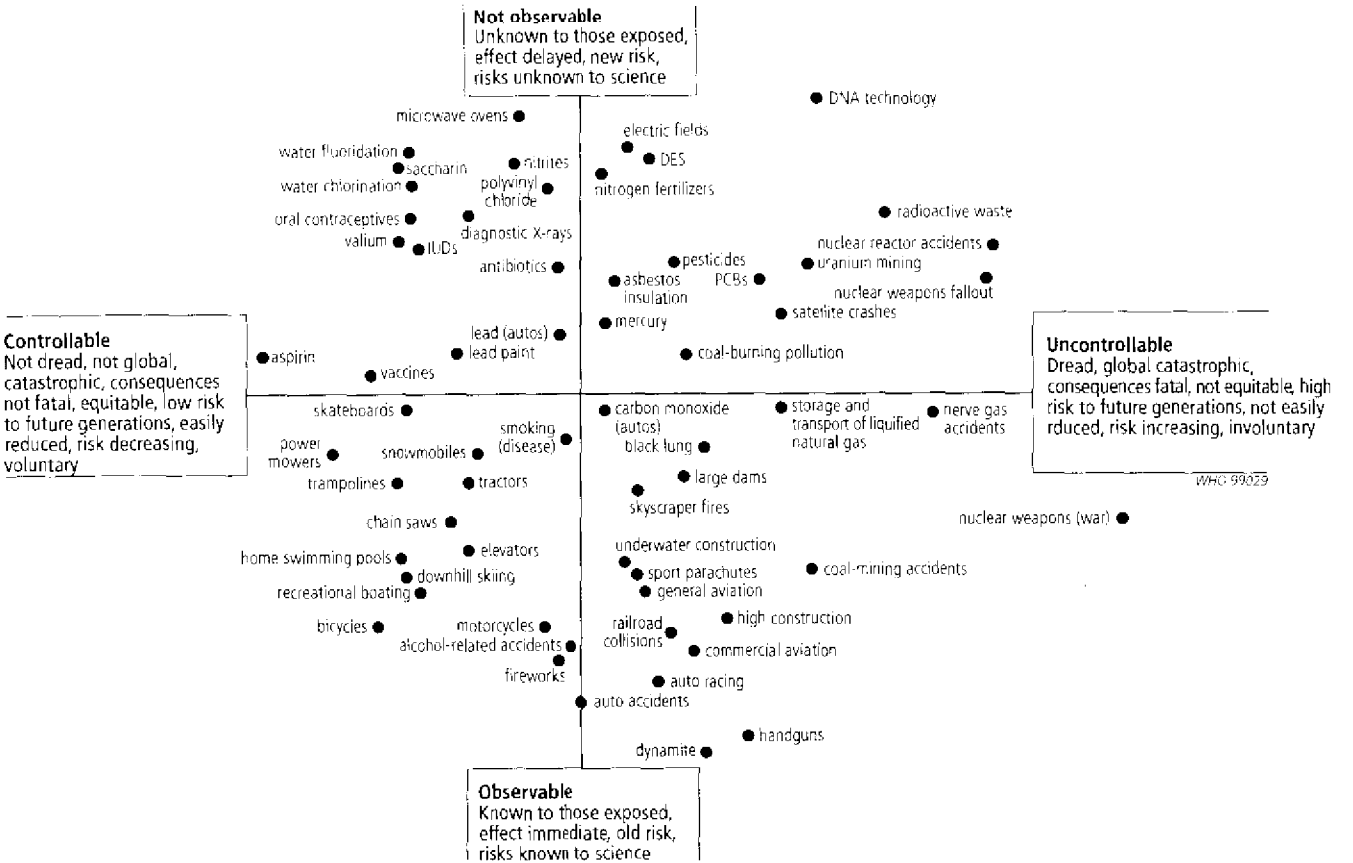

Fig. 3. Public perception of risks in terms of risk space quadrants (Morgan, 1993)

Table 3. Qualitative factors affecting risk perception and evaluation (from: US NRC, 1989)

Factor	Conditions associated with increased public concern	Conditions associated with decreased public concern
Catastrophic potential	Fatalities and injuries grouped in time and space	Fatalities and injuries scattered and random
Familiarity	Unfamiliar	Familiar
Understanding	Mechanisms or process not understood	Mechanisms or process understood
Controllability (personal)	Uncontrollable	Controllable
Voluntariness of exposure	Involuntary	Voluntary
Effects on children	Children specifically at risk	Children not specifically at risk
Effects manifestation	Delayed effects	Immediate effects
Effects on future generations	Risk to future generations	No risk to future generations
Victim identity	Identifiable victims	Statistical victims
Dread	Effects dreaded	Effects not dreaded
Trust in institutions	Lack of trust in responsible institutions	Trust in responsible institutions
Media attention	Much media attention	Little media attention
Accident history	Major and sometimes minor accidents	No major or minor accidents
Equity	Inequitable distributions of risks and benefits	No major or minor accidents
Benefits	Unclear benefits	Clear benefits
Reversibility	Effects irreversible	Effects reversible
Origin	Caused by human actions or failures	Caused by acts of nature or God

Table 4. Characteristics of risk (from: Scala, 1991)

Characteristic	Description	Level	Examples
Knowledge	Society's awareness of risk from activity	Little known Much known	Food additives Alcoholic drinks
Newness	Extent of societal experience	Old New	Guns Space travel
Voluntariness	Does individual have a choice about exposure to risk	Not voluntary Voluntary	Crime Rock climbing
Control	Can an individual control exposure, protect himself or control consequences	Risk not controlled by skill or diligence Risk controlled by skill or diligence	Natural disasters Smoking
Dreadedness	How much is risk or its consequences feared	People do not dread People have great dread	Vaccination Nerve gas
Catastrophic potential	Chance of widespread disastrous outcome	Not likely Likely	Sunbathing War
Equity	Are the benefits and risk shared equally	Distributed unequally Distributed equally	Hazardous dump Skiing

1993). Risk communication is an interactive process of exchange of information and opinion among individuals, groups and institutions involving multiple messages about the nature of risk and other messages, not strictly about risk, that express concerns, opinions or reactions to risk messages or to legal and institutional arrangements for risk management (US NRC, 1989).

Until the mid-1980s, there was little research on communicating risk to the public. There is now a reasonable consensus on the optimum basic elements of risk communication. These efforts should be more systematically oriented to the intended audience, addressing the audience's perspectives and concerns. To the greatest extent possible, openness, not minimizing the existence of uncertainty, and discussion of data gaps and areas of significant disagreement among experts is recommended. The acceptance of any risk is more dependent on public confidence in risk management than on quantitative estimates of risk.

Although there is as yet no widely agreed structured knowledge on communication about chemical hazards, analyses of risk communication efforts and case studies suggest that risk communication problems arise from message, source, channel and receiver problems (Cohrssen & Covello, 1989). Message problems relate primarily to deficiencies in scientific understanding leading to large uncertainties in risk estimates or highly technical risk analyses that are unintelligible to lay persons. Source problems include disagreements among scientific experts, failures to disclose limitations of risk assessments and resulting uncertainties, and limited understanding of the concerns and values of public groups and bureaucratic presentation. Channel problems include selective and biased media reporting that emphasizes drama, wrongdoing, disagreement, conflict and oversimplification, distortion, and inaccuracy in interpreting technical risk information. Receiver problems include inaccurate perception of levels of risk, strong beliefs and opinions that are resistant to change, and demands for scientific certainty.

There is a clear need to educate the public, including community leaders, workers and school children, to enhance awareness so that they can take voluntarily the action required to reduce or avoid risks associated with exposure to chemicals in the workplace and general environments (e.g., indoor air pollutants, pesticides and household chemicals).

6.3.6 Economic factors

Unlike regulation, which involves strict criteria to be enforced by regulatory agencies, economic approaches to risk management rely largely on economic incentives to reduce the levels of pollutants introduced into the environment (Krewski et al., 1989; Somers, 1993).

The OECD since 1972 has espoused the "Polluter Pays Principle" (PPP) concept, with the goal of maintaining equitable trading practices by encouraging polluters to reduce emissions. However, it is recognized that the consumer ultimately pays the cost required to accomplish environmental improvements. The main types of economic instruments in use in OECD countries include charges, subsidies, deposit-refund schemes, market creation arrangements and financial enforcement incentives (OECD, 1991b). In 1989, the OECD adopted a Recommendation on the Application of the PPP to Accidental Pollution, which links the economic principle and the legal principle to damage compensation (OECD, 1991b).

6.3.6.1 *Cost–benefit analyses*

Traditionally, risk reduction has not included a thorough analysis of costs and benefits (Hammond & Coppock, 1990). Indeed, there is no widely adopted framework for cost–benefit.

As an example, three major categories of costing relationships are typically employed in risk reduction by the US EPA, depending on the situation:

a) benefit/cost analysis weighs the cost of control against monetary benefits of control;

b) risk/benefit analysis weighs the economic benefits of a polluting activity against the risks to health and the environment;

c) cost-effectiveness analysis accepts the desirability of regulation and identifies the least-cost solution to achieve a given goal, such as a pollution discharge standard (Ris & Preuss, 1988).

The US EPA estimated that the annual compliance cost for USA federal environmental regulations in 1990 was about 2.1% of the gross national product (GNP of about 6 trillion dollars). This is expected to

increase to approximately 2.8% of the GNP by the year 2000 (ILSI/National Safety Council, 1993). The benefits of regulation such as improved quality of life and cleaner environment are often difficult to quantify in contrast to the enormous costs often cited for regulatory compliance.

There is broad diversity of opinion as to how costs should be considered in risk management decisions. Key questions include: How much can society afford to spend to reduce risks? What is an acceptable cost per life saved? How should costs be factored into priority-setting processes? Future success in risk management may to a large degree depend on ways to weigh benefits and costs and to strike the appropriate balance in defining how fast to pursue risk regulations (ILSI/National Safety Council, 1993; Wiener, 1993).

6.3.7 Political factors

Political factors often have an impact on national and local priorities, drafting of regulatory statutes and introduction of resulting risk reduction measures. Trade barriers and global competition also have a considerable impact on risk reduction. For example, in Canada the decision in 1980 to ban the sale of urea–formaldehyde foam insulation (UFFI) led to unprecedented public anger (and anxiety and resentment), great government expense, the longest civil suit in Canadian history, and appreciable political consequences. After an 8-year legal trial, it was concluded that there was not sufficient scientific evidence to substantiate the reported health problems of UFFI home owners (Somers, 1993).

In 1977, the US Food & Drug Administration (FDA), reacting to studies that reported the artificial sweetening agent saccharin to be a bladder carcinogen in rodent feeding studies, proposed to ban the agent under the Delaney Amendment ("zero-risk") requirement. The Congress of the USA in November 1977, reacting to the overwhelming public outcry in support of unrestricted use of saccharin, enacted the Saccharin Study and Labeling Act (SSLA), which prevented the FDA from banning saccharin based on the information that was then available. This made it clear that the public is willing to accept certain risks from food additives if it perceives that the benefits are high enough and, possibly, that the risks are low enough (Flamm & Lorentzen, 1988).

6.3.8 Regulatory limits

Traditionally, one avenue of protection of human health has been through the establishment of exposure limits (variously referred to as standards, quality criteria, etc.). These are established in a two-step process, the first involving consideration of the health-based scientific data and the second involving establishment of regulatory limits, taking into account the health-based recommendation along with other factors.

Examples of health-based exposure guidelines include the Acceptable Daily Intake (ADI), Tolerable Daily Intake (TDI), Provisional Tolerable Weekly Intake (PTWI), and health-based Maximum Allowable Concentrations (MAC). Acceptable/Tolerable Intakes are the amounts of a food additive, contaminant, pesticide or veterinary drug residue, expressed on a body weight basis, that can be ingested for a lifetime without appreciable risk to health. The term ADI is commonly used for additives to food since they impart some beneficial characteristic (and hence are considered "acceptable") while a TDI commonly refers to environmental contaminants which are undesirable. Maximum Allowable Concentrations are either a time-weighted average concentration of a substance in a medium of exposure that does not present appreciable hazard for continuing exposure or an upper limit (ceiling value) which, if exceeded, will have adverse consequences for health. Often, health-based guidelines are considered, along with other factors (i.e., technological, socioeconomic, feasibility, enforcement), to develop operational regulatory limits such as the Maximum Residue Level (MRL) for pesticides or veterinary drugs, MAC in exposure media and workplaces, occupational Threshold Limit Values (TLV), Maximum Workplace Concentrations (MAK), Occupational Exposure Limits (OEL), Air Quality Standards (AQS), Water Quality Standards (WQS) or Maximum Use Levels.

Some media of (direct and indirect) exposure and associated limits are listed below:

Food

- limits for food additives, contaminants, pesticide residues, veterinary drug residues
- limits for certain chemicals in food packaging materials

- limits for additives and contaminants in animal feed

Cosmetics and other consumer products

- limits for additives and contaminants in cosmetic products (these include soap and toothpaste)
- limits for other consumer products such as children's toys, paints and solvents

Water

- drinking-water quality standards
- water quality standards for surface water
- water quality standards for fresh water used for fishing
- water quality standards for estuarine and marine waters
- aqueous effluent standards for industrial effluents and sewage treatment outfall
- guideline limits for the use of waste water in agriculture and aquaculture

Air

- air quality (ambient or indoor) limits for gases, vapours, fibres, particulates
- air quality standards for gaseous or smoke emissions from industries

Occupational

- occupational exposure limits for gases, vapours, dusts, aerosols in workplace air and substances absorbed through the skin, mucous membranes or alimentary tract
- regulatory limits for exposure can be based on appropriate biomarkers

Soil

- limits for certain chemicals in soil

Agricultural chemicals

- limits for certain contaminants in agrochemicals (fertilizers)
- limits for application rates of pesticides

Chemical waste

- limits for disposal of chemicals as waste products
- waste (including liquid and solid)
- chemical (including mixed industrial), dumps, surface water and deep well injection
- municipal surface and groundwater contamination, use of sludge in agriculture
- atmospheric effluents and residual ash from incineration

The two stages and their outputs should not be confused. The outputs are frequently expressed in different units. For example, considering pesticide residues in food crops, the ADI is a daily dose expressed in mg/kg body weight (per day being implicit) whereas the MRL is a concentration on the crop expressed in mg/kg of the produce. The MRL may be derived on the basis of Good Agricultural Practice and, if adhered to, would not result in the ADI being exceeded even if all the designated crop contained the pesticide at the MRL (an unlikely postulate). Clearly, to arrive at this conclusion requires information on daily intakes of the commodities carrying the residue.

6.4 Risk management options

Risk managers can intervene at many points:

a) to prevent the process producing the risk
b) to reduce or eliminate exposures
c) to modify the effects
d) to alter perceptions or valuation, through education and public relations
e) to compensate for damage after the fact (Morgan, 1993).

6.4.1 Risk reduction

Risk reduction goals can vary considerably and can also be hampered by the fragmented regulatory structure enforcing environmental laws in many countries. For example, in the USA, the

regulatory approach to risk reduction depends upon whether a chemical is a food additive, a food contaminant, a pesticide, a drinking-water contaminant, an air pollutant, or several of these (Rodricks, 1992). Increasingly, however, national legislation (such as the Canadian Environmental Protection Act) that allows for introduction of control measures for chemicals in a variety of media is being introduced. Essentially, such legislation enables the development of control measures in the medium that will contribute most significantly to reduction of risk. The existing substances regulation of the European Union also provides the opportunity for concerted action based on evaluation of risks for different scenarios and routes of exposure (EEC Council Regulation No.793/93) (EC, 1993).

However, there is no clear consensus on what is considered a risk of concern. While target risk levels are embodied in some national legislation, other countries recommend that exposure be reduced as low as possible for effects for which it is assumed that there is no threshold.

It is also well recognized that different countries, as well as different agencies within the same country, often come to different conclusions in the manner in which they judge and manage a health risk employing basically the same scientific data (Nilsson et al., 1993; Somers, 1993). Nilsson et al. (1993) found that 11 countries regulated the same pesticides to different degrees, which should not be too surprising recognizing the differing economic interests and statutes (Somers, 1993).

6.4.1.1 *Technology-based criteria*

Technology-based criteria for risk reduction are not based on costs, benefits or rights, but rather the level of technology to control certain risks. Regulations based on these criteria typically mandate "the best available technology" (BAT) or emissions that are "as low as reasonably achievable". Such rules can be difficult to apply because people seldom agree on the definition of "available" or "reasonably achievable" (Morgan, 1993). Similar difficulties can arise with the implementation of "good agricultural practice", "technically achievable" and "as far as may be reasonably practicable".

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APPENDIX 1. PREAMBLE TO THE IARC MONOGRAPHS

The Preamble to the Monographs sets out the objective and scope of the evaluation programme, the procedures used when making assessments, and the types of evidence considered and criteria used in reaching the final evaluations. The list of contents is given here as is the full text referring to the Background and Evaluation sections. Full text of the Preamble should always be used when referring to the list of evaluations provided.

Background

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme to evaluate the carcinogenic risk of chemicals to humans and to produce monographs on individual chemicals. The *Monographs* programme has since been expanded to include consideration of exposures to complex mixtures of chemicals (which occur, for example, in some occupations and as a result of human habits) and of exposures to other agents, such as radiation and viruses. With Supplement 6 (IARC, 1987a), the title of the series was modified from *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* to *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, in order to reflect the widened scope of the programme.

The criteria established in 1971 to evaluate carcinogenic risk to humans were adopted by the working groups whose deliberations resulted in the first 16 volumes of the *IARC Monographs series*. Those criteria were subsequently updated by further ad-hoc working groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987b, 1988, 1991; Vainio et al., 1992).

Evaluation

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent, mixture or exposure circumstance to a higher or lower category than a strict interpretation of these criteria would indicate.

(*a*) *Degrees of evidence for carcinogenicity in humans and in experimental animals and supporting evidence*

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency) nor to the mechanisms involved. A classification may change as new information becomes available.

An evaluation of degree of evidence, whether for a single agent or a mixture, is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of degree of evidence.

(i) Carcinogenicity in humans

The applicability of an evaluation of the carcinogenicity of a mixture, process, occupation or industry on the basis of evidence from epidemiological studies depends on the variability over time and place of the mixtures, processes, occupations and industries. The Working Group seeks to identify the specific exposure, process or activity which is considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is,

a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent, mixture or exposure circumstance and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that human beings are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent, mixture or exposure circumstance and any studied cancer at any observed level of exposure. A conclusion of 'evidence suggesting lack of carcinogenicity' is inevitably limited to the cancer sites, conditions and levels of exposure and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

(ii) Carcinogenicity in experimental animals

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent or mixture and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two

or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; or (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (c) the agent or mixture increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent or mixture is not carcinogenic. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the species, tumour sites and levels of exposure studied.

(*b*) *Other data relevant to the evaluation of carcinogenicity and its mechanisms*

Other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is then described. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and pharmacokinetics, physicochemical parameters and analogous biological agents.

Data relevant to mechanisms of the carcinogenic action are also evaluated. The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is assessed, using terms such as weak, moderate or strong. Then, the Working Group assesses if that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans come from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(*c*) *Overall evaluation*

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity to humans of an agent, mixture or circumstance of exposure.

An evaluation may be made for a group of chemical compounds that have been evaluated by the Working Group. In addition, when supporting data indicate that other, related compounds for which there is no direct evidence of capacity to induce cancer in humans or in animals may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of compounds if the strength of the evidence warrants it.

The agent, mixture or exposure circumstance is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent, mixture or exposure circumstance is a matter of scientific judgement, reflecting the strength of the evidence derived from studies in humans and in experimental animals and from other relevant data.

- *Group 1: The agent (mixture) is carcinogenic to humans.*
  The exposure circumstance entails exposures that are carcinogenic to humans.

This category is used when there is *sufficient evidence* of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence in humans is less than sufficient but there is *sufficient evidence* of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

- *Group 2*

This category includes agents, mixtures and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents, mixtures and exposure circumstances are assigned to either group 2A (probably carcinogenic to humans) or group 2B (possibly carcinogenic to humans) on the basis of epidemiological and experimental evidence of carcinogenicity and other relevant data.

- *Group 2A: The agent (mixture) is probably carcinogenic to humans.*
  The exposure circumstance entails exposures that are probably carcinogenic to humans.

This category is used when there is *limited evidence* of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is inadequate evidence of carcinogenicity in humans and *sufficient evidence* of carcinogenicity

in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of limited evidence of carcinogenicity in humans.

- *Group 2B: The agent (mixture) is possibly carcinogenic to humans.*
  The exposure circumstance entails exposures that are possibly carcinogenic to humans.

This category is used for agents, mixtures and exposure circumstances for which there is *limited evidence* of carcinogenicity in humans and less than *sufficient evidence* of carcinogenicity in experimental animals. It may also be used when there is *inadequate evidence* of carcinogenicity in humans but there is *sufficient evidence* of carcinogenicity in experimental animals. In some instances, an agent, mixture or exposure circumstance for which there is *inadequate evidence* of carcinogenicity in humans but *limited evidence* of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

- *Group 3: The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.*

This category is used most commonly for agents, mixtures and exposure circumstances for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals.

Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents, mixtures and exposure circumstances that do not fall into any other group are also placed in this category.

- *Group 4: The agent (mixture) is probably not carcinogenic to humans.*

This category is used for agents or mixtures for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents or mixtures for which there is *inadequate evidence* of carcinogenicity in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

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APPENDIX 2. OECD'S GUIDELINES FOR THE TESTING OF CHEMICALS

(from http://www.oecd.org/ehs/test/health.htm)

1. Adopted Test Guidelines

TG **401** Acute Oral Toxicity *(Updated Guideline, adopted 24th February 1987)*

TG **402** Acute Dermal Toxicity *(Updated Guideline, adopted 24th February 1987)*

TG **403** Acute Inhalation Toxicity *(Original Guideline, adopted 12th May 1981)*

TG **404** Acute Dermal Irritation/Corrosion *(Updated Guideline, adopted 17th July 1992)*

TG **405** Acute Eye Irritation/Corrosion *(Updated Guideline, adopted 24th February 1987)*

TG **406** Skin Sensitisation *(Updated Guideline, adopted 17th July 1992)*

TG **407** Repeated Dose 28-day Oral Toxicity Study in Rodents *(Updated Guideline, adopted 27th July 1995*

TG **408** Subchronic Oral Toxicity – Rodent: 90-day Study *(Original Guideline, adopted 12th May 1981)*

TG **409** Subchronic Oral Toxicity – Non-Rodent: 90-day Study *(Original Guideline, adopted 12th May 1981)*

TG **410** Repeated Dose Dermal Toxicity: 21/28-day Study *(Original Guideline, adopted 12th May 1981)*

TG **411** Subchronic Dermal Toxicity: 90-day Study *(Original Guideline, adopted 12th May 1981)*

TG **412** Repeated Dose Inhalation Toxicity: 28-day or 14-day Study *(Original Guideline, adopted 12th may 1981)*

TG **413** Subchronic Inhalation Toxicity: 90-day Study *(Original Guideline, adopted 12th May 1981*

TG **414** Teratogenicity *(Original Guideline, adopted 12th May 1981*

TG **415** One-Generation Reproduction Toxicity Study *(Original Guideline, adopted 26th May 1983)*

TG **416** Two-Generation Reproduction Toxicity Study *(Original Guideline, adopted 26th May 1983*

TG **417** Toxicokinetics *(Updated Guideline, adopted 4th April 1984)*

TG **418** Delayed Neurotoxicity of Organophosphorus Substances Following Acute Exposure *(Updated Guideline, adopted 27th July 1995)*

TG **419** Delayed Neurotoxicity of Organophosphorus Substances: 28-day Repeated Dose Study *(Updated Guideline, adopted 27th July 1995*

TG **420** Acute Oral Toxicity – Fixed Dose Method *(Original Guideline, adopted 17th July 1992*

TG **421** Reproduction/Developmental Toxicity Screening Test *(Original Guideline, adopted 27th July 1995)*

TG **422** Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test *(Original Guideline, adopted 22nd March 1996)*

TG **423** Acute Oral toxicity – Acute Toxic Class Method *(Original Guideline, adopted 22nd March 1996)*

TG **424** Neurotoxicity Study in Rodents *(Original Guideline, adopted 21st July 1997*

TG **451** Carcinogenicity Studies *(Original Guideline, adopted 12th May 1981)*

TG **452** Chronic Toxicity Studies *(Original Guideline, adopted 12th May 1981)*

TG **453** Combined Chronic Toxicity/Carcinogenicity Studies *(Original Guideline, adopted 12th May 1981*

TG **471** Bacterial Reverse Mutation Test *(Updated Guideline, adopted 21st July 1997*

TG **473** *In vitro* Mammalian Chromosomal Aberration Test *(Updated Guideline, adopted 21st July 1997*

TG **474** Mammalian Erythrocyte Micronucleus Test *(Updated Guideline, adopted 21st July 1997)*

TG **475** Mammalian Bone Marrow Chromosomal Aberration Test *(Updated Guideline, adopted 21st July 1997)*

TG **476** *In vitro* Mammalian Cell Gene Mutation Test *(Updated Guideline, adopted 21st July 1997)*

TG **477** Genetic Toxicology: Sex-Linked Recessive Lethal Test in *Drosophila melanogaster (Updated Guideline, adopted 4th April 1984)*

TG **478** Genetic Toxicology: Rodent Dominant Lethal Test *(Updated Guideline, adopted 4th April 1984)*

TG **479** Genetic Toxicology: In vitro Sister Chromatid Exchange Assay in Mammalian Cells *(Original Guideline, adopted 23rd October 1986)*

TG **480** Genetic Toxicology: Saccharomyces cerevisiae, Gene Mutation Assay (Original Guideline, adopted 23rd October 1986)

TG **481** Genetic Toxicology: Saacharomyces cerevisiae, Miotic Recombination Assay (Original Guideline, adopted 23rd October 1986)

TG **482** Genetic Toxicology: DNA Damage and Repair, Unscheduled DNA Synthesis in Mammalian Cells *in vitro (Original Guideline, adopted 23rd October 1986)*

TG **483** Mammalian Spermatogonial Chromosome Aberration Test (Original Guideline, adopted 21st July 1997) *TG* **484** Genetic Toxicology: Mouse Spot Test *(Original Guideline, adopted 23rd October 1986)*

TG **485** Genetic Toxicology: Mouse Heritable Translocation Assay *(Original Guideline, adopted 23rd October 1986)*

TG **486** Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells *in vivo (Original Guideline, adopted 21st July 1997)*

2. Draft Test Guidelines

TG **403** Acute Inhalation Toxicity *(Draft Updated Guideline, August 1996)*[a]

TG **408** Repeated Dose 90-Day Oral Toxicity Study in Rodents *(Draft Updated Guideline, May 1998, EPOC Document)*[a]

TG **409** Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents *(Draft Updated Guideline, May 1998, EPOC Document)*[a]

TG **414** Prenatal Developmental Toxicity Study *(Draft Updated Guideline, March 1998)*[a]

TG **416** Two-Generation Reproduction Toxicity Study *(Draft Updated Guideline, April 1996)*[a]

TG **425** Acute Oral Toxicity: Up-and-Down Procedure *(Draft New Guideline, May 1998, EPOC Document)*[a]

Somatic Mutation and Recombination Tests (SMART) in *Drosophila melanogaster (Draft New Guideline, May 1994)*[a]

Percutaneous Absorption: *in vitro* Method *(Draft New Guideline, May 1996)*[a]

Percutaneous Absorption: *in vivo* Method *(Draft New Guideline, June 1996)*[a]

Acute Dermal Photoirritation Screening Test *(Draft New Guideline, February 1995)*[a]

Acute Dermal Photoirritation Dose-Response Test *(Draft New Guideline, February 1995)*[a]

In Vitro Syrian Hamster Embryo (SHE) Cell Transformation Assay *(Draft New Guideline, March 1996)*[a]

Acute Dermal Irritation Study in Human Volunteers *(Draft New Guideline, April 1997)*[a]

[a] Available in Portable Document Format or Word 6 Format.

1. RÉSUMÉ

La maîtrise des risques résultant d'une exposition à des produits chimiques (la sécurité chimique) implique avant tout une évaluation scientifique – dans le meilleur des cas, quantitative – des effets potentiels en fonction de l'intensité de l'exposition (l'évaluation du risque). En s'appuyant sur les résultats de cette évaluation et compte tenu d'un certain nombre d'autres facteurs, il est possible d'entamer un processus décisionnel visant à éliminer ou, en cas d'impossibilité, à réduire au minimum, le ou les risques imputables à la ou aux substances chimiques en cause (la gestion du risque).

L'évaluation du risque constitue le cadre conceptuel dans lequel peut s'exercer un processus ordonné d'examen des données permettant d'apprécier les conséquences sanitaires ou écologiques de l'exposition à telle ou telle substance. Aux Etats-Unis, l'Académie nationale des sciences suit, pour ses évaluations du risque, une démarche qui a fait la preuve de son utilité (US NAS, 1983). Elle distingue quatre phases distinctes dans le processus d'évaluation: la reconnaissance du danger, l'évaluation de la relation dose–réponse, l'évaluation de l'exposition et la caractérisation du risque.

La reconnaissance du danger a pour objet d'apprécier les éléments qui tendent à prouver l'existence d'effets indésirables pour l'homme, en s'appuyant sur l'ensemble des données toxicologiques disponibles et sur tout ce que l'on peut savoir du mode d'action du produit en cause. Il s'agit essentiellement de répondre à deux questions, à savoir 1) si l'agent en cause représente un danger pour l'Homme et 2) dans quelles circonstances ce danger est susceptible de se manifester. La reconnaissance du danger repose sur l'analyse de diverses données qui peuvent aller d'observations sur l'Homme à l'étude des relations entre l'activité de la substance et sa structure. Il doit alors être possible de se prononcer scientifiquement sur la question de savoir si la substance à expertiser peut, dans des conditions d'exposition données, avoir des effets indésirables sur la santé humaine. En général, les effets toxiques s'observent au niveau d'un ou de plusieurs **organes cibles**. Souvent, on s'efforce d'observer les divers points d'aboutissement de l'action toxique de la substance. On détermine alors **l'effet critique**, qui représente habituellement le

premier effet indésirable important à apparaître lorsque la dose augmente.

L'évaluation de la relation dose–réponse consiste à établir la relation qui existe entre la dose de produit administrée ou reçue et la fréquence d'un effet nocif. Pour presque tous les types d'effets toxiques (c'est-à-dire organospécifiques, neurologiques ou comportementaux, immunologiques, cancérogènes non génotoxiques, génésiques ou développementaux), on estime généralement qu'il existe une dose ou une concentration au-dessous de laquelle aucun effet indésirable ne se produit (c'est-à-dire qu'il existe un seuil de toxicité). Pour d'autres types d'effets toxiques, on suppose qu'il existe une probabilité d'action toxique quelle que soit l'intensité de l'exposition (autrement dit qu'il n'y a pas de seuil de toxicité). A l'heure actuelle, cette dernière hypothèse s'applique en général essentiellement aux effets mutagènes et aux effets cancérogènes génotoxiques.

Si l'on suppose l'existence d'un seuil (par exemple, dans le cas d'effets non cancérogènes ou d'effets cancérogènes non génotoxiques), on a l'habitude de déterminer le niveau d'exposition au-dessous duquel on estime nulle la probabilité d'effets toxiques et que l'on exprime par la dose sans effet nocif observable ou NOAEL, compte tenu d'un certain nombre de facteurs d'incertitude (il s'agit d'une valeur approchée du seuil de toxicité). On peut aussi déterminer de combien la dose (la plus faible) sans effet nocif observable dépasse le niveau d'exposition estimé (c'est-à-dire la "marge de sécurité") en fonction des diverses sources d'incertitude. C'est une méthode que l'on a pu souvent qualifier d'"évaluation du degré de sécurité". Par conséquent la dose que l'on peut considérer en première approximation comme le seuil de toxicité, c'est-à-dire la NOAEL, constitue la dose critique. On a toutefois de plus en plus tendance à utiliser la "dose de référence", une estimation (ou la limite inférieure de l'intervalle de confiance correspondant), obtenue par modélisation, de la dose produisant l'effet critique avec une fréquence particulière (par ex. 5%) pour l'évaluation quantitative de la relation dose–réponse dans le cas de ce genre d'effets.

Il n'y a pas de véritable consensus au sujet de la méthodologie à adopter pour évaluer le risque dans le cas de substances pour

lesquelles il pourrait ne pas exister de seuil pour l'effet critique (par exemple les cancérogènes génotoxiques et les mutagènes agissant au niveau des cellules germinales). De fait, on utilise en pareil cas un certain nombre de méthodes qui reposent en grande partie sur la caractérisation de la relation dose-réponse. Dans ces conditions, ce qui compte, ce sont les points expérimentaux qui définissent la pente de la courbe dose–réponse (et non pas la NOAEL, qui constitue une première approximation de la valeur du seuil).

La troisième phase du processus consiste dans l'**évaluation de l'exposition**. Elle a pour objet de déterminer la nature et le degré du contact qui a eu lieu ou qui pourrait avoir lieu avec telle ou telle substance chimique dans diverses conditions. Différentes méthodes peuvent être utilisées pour procéder à ce type d'évaluation. En général il s'agit de méthodes directes ou indirectes comportant la mesure des concentrations dans l'environnement et celle de l'exposition individuelle ou de marqueurs biologiques. On fait souvent appel aussi à des modèles et à des questionnaires. L'évaluation de l'exposition nécessite la détermination des émissions de produits chimiques, des voies qu'ils empruntent et de la vitesse de leur déplacement, de même que leur transformation ou décomposition, afin d'évaluer la concentration à laquelle les populations humaines ou les différents compartiments de l'environnement (eau, air, sol) peuvent être exposés.

Selon le but de l'évaluation, le résultat numérique peut se présenter sous la forme d'une estimation de l'intensité, de la vitesse,de la durée ou de la fréquence du contact ou encore d'une estimation de la dose (quantité de produit qui franchit effectivement la limite). Il importe de noter que c'est la dose interne, et non le niveau d'exposition externe, qui détermine l'effet toxique d'une exposition donnée.

La caractérisation du risque constitue la phase finale du processus d'évaluation du risque. Elle a pour but de faciliter la tâche de ceux qui ont la responsabilité de gérer ce risque en leur fournissant, en langage ordinaire, les données scientifiques essentielles et les principes de base sur lesquels appuyer leurs décisions. En particulier, on leur donne une évaluation du risque pour la santé humaine dans des situations d'exposition appropriées. La caractérisation du risque revient donc à

évaluer et à intégrer les données scientifiques disponibles pour déterminer la nature, l'importance – et souvent l'ampleur- du risque biologique ou écologique qu'une exposition à tel ou tel produit peut faire courir dans des circonstances précises, compte tenu des incertitudes qui lui sont attachées.

Par "gestion du risque" on entend l'ensemble des activités à mettre en oeuvre pour pouvoir décider si le risque associé à une substance donnée appelle une élimination ou une réduction. Les stratégies et les options qui s'offrent en la matière peuvent être classées en gros selon leur nature en réglementaires, non réglementaires, économiques, conseillées, ou technologiques, les unes n'excluant pas forcément les autres. Ainsi, les mandats législatifs (les directives réglementaires), les considérations politiques, les valeurs socioéconomiques, le coût, la faisabilité technique, les populations exposées au risque, la durée et l'ampleur du risque et les conséquences possibles sur les échanges commerciaux internationaux, constituent toute une panoplie de facteurs dont il pourra être tenu compte dans la politique ou la réglementation finale. Les déterminants fondamentaux de la décision tels que la taille de la population, les ressources, les dépenses à envisager pour atteindre les objectifs de même que la valeur scientifique de l'évaluation du risque et des options opérationnelles ultérieures varient considérablement d'un contexte à l'autre. Il est également admis que la gestion des risques est une procédure complexe et de nature pluridisciplinaire, qui se présente rarement sous une forme codifiée ou uniforme, qu'elle est souvent peu structurée, mais qu'elle est néanmoins susceptible de prendre en compte des données changeantes émanant des sources les plus diverses. On estime de plus en plus que la perception du risque et le problème de la communication sont aussi des éléments importants à prendre en considération si l'on veut que les décisions soient acceptées par le public le plus large possible.

Les produits chimiques sont devenus indispensables à l'Homme, qu'il s'agisse de lui permettre de mener à bien ses activités et son développement, de prévenir et de combattre de nombreuses maladies et d'accroître les rendements agricoles. En dépit de tous ces avantages, les produits chimiques, surtout s'ils sont mal utilisés, peuvent avoir des effets néfastes sur la santé humaine et sur l'environnement.

L'utilisation généralisée de ces produits dans l'ensemble du monde augmente le risque d'effets indésirables. On peut s'attendre à ce que les industries chimiques poursuivent leur croissance dans les pays développés comme dans les pays en développement. Compte tenu de cela, l'évaluation et la gestion des risques résultant de l'exposition aux produits chimiques apparaissent comme des priorités de tout premier plan dans la recherche d'un développement durable.

1. RESUMEN

El control de los riesgos de exposición a productos químicos (seguridad química) requiere en primer lugar una evaluación científica, idealmente cuantitativa, de los efectos potenciales con determinadas concentraciones de exposición (evaluación del riesgo). Tomando como base los resultados de la evaluación del riesgo y teniendo en cuenta otros factores, se puede comenzar un proceso de adopción de decisiones encaminado a eliminar o, si esto no fuera posible, reducir al mínimo el riesgo de exposición a los productos químicos objeto de examen (evaluación del riesgo).

La evaluación del riesgo es un marco conceptual que proporciona el mecanismo que permite un examen estructurado de la información de interés para la estimación de los resultados en la salud o en el medio ambiente. En la realización de las evaluaciones del riesgo, el modelo de la Academia Nacional de Ciencias ha resultado un instrumento útil (US NAS, 1983). En este modelo el proceso de evaluación del riesgo se divide en cuatro etapas distintas: identificación del peligro, evaluación de la relación dosis–respuesta, evaluación de la exposición y caracterización del riesgo.

La identificación del peligro tiene por objeto evaluar la importancia de las pruebas relativas a los efectos adversos en el ser humano, basándose en la evaluación de todos los datos disponibles sobre la toxicidad y el mecanismo de acción. Está concebida para abordar fundamentalmente dos cuestiones:1) si un agente puede representar un peligro para la salud de los seres humanos y 2) en qué circunstancias puede manifestarse un peligro identificado. La identificación del peligro se basa en el análisis de diversos datos, que pueden ir desde las observaciones en el ser humano hasta el análisis de las relaciones existentes entre la estructura y la actividad. El resultado de la práctica de identificación del peligro es un dictamen científico en cuanto a si el producto químico evaluado puede, en determinadas condiciones de exposición, causar un efecto adverso en la salud de los seres humanos. En general, se observa toxicidad en un **órgano destinatario** o en más. Con frecuencia se detectan efectos finales múltiples tras la exposición a un producto químico concreto. Se

determina el **efecto crítico**, que normalmente es el primer efecto adverso importante que se produce al aumentar la dosis.

La evaluación de la relación dosis–respuesta es el proceso de caracterización de la relación existente entre la dosis de un producto administrado o recibido y la incidencia de un efecto adverso en la salud. En la mayor parte de los tipos de efectos tóxicos (es decir, específicos de órganos, neurológicos/del comportamiento, inmunitarios, carcinogénesis no genotóxica, en la reproducción o en el desarrollo), se suele considerar que existe una dosis o concentración por debajo de la cual no se producen efectos adversos (es decir, un umbral). Para otros tipos de efectos tóxicos, se supone que existe alguna probabilidad de peligro en todas las concentraciones de exposición (es decir, que no existe un umbral). En la actualidad, el último supuesto se aplica fundamentalmente a la mutagénesis y la carcinogénesis genotóxica.

Si se supone la existencia de un umbral (por ejemplo, para los efectos no neoplásicos y para los carcinógenos no genotóxicos), normalmente se estima que existe un nivel de exposición por debajo del cual no hay efectos adversos, basado en la concentración sin efectos adversos observados (NOAEL) (aproximación del umbral) y en factores de incertidumbre. Otra posibilidad consiste en examinar la magnitud en la cual la concentración sin efectos adversos observados (o efectos mínimos) (NOAEL o LOAEL) es superior a la exposición estimada (es decir, el "margen de seguridad"), teniendo en cuenta distintas fuentes de incertidumbre. Anteriormente, este método se ha descrito con frecuencia como una "evaluación de la seguridad". Por consiguiente, es fundamental la concentración que se puede considerar como una primera aproximación del umbral, es decir la NOAEL. Sin embargo, en la evaluación cuantitativa de la relación dosis–respuesta se propone cada vez más el uso de la "dosis de referencia", estimación derivada de un modelo (o su límite de confianza más bajo) de un nivel de incidencia determinado (por ejemplo, del 5%) para el efecto crítico.

No hay un consenso claro sobre la metodología apropiada para la evaluación del riesgo de los productos químicos sin umbral para el efecto crítico (es decir, carcinógenos genotóxicos y mutágenos de células germinales). Es más, en tales casos se han adoptado diversos

métodos basados fundamentalmente en la caracterización de la relación dosis–respuesta. Por consiguiente, los puntos críticos de los datos son los que definen la pendiente de la relación dosis–respuesta (más que la NOAEL, que es la primera aproximación de un umbral).

La tercera etapa en el proceso de evaluación del riesgo es la **evaluación de la exposición**, que tiene por objeto determinar la naturaleza y la amplitud del contacto experimentado o previsto con las sustancias químicas en distintas condiciones. Se pueden utilizar numerosos métodos para realizar las evaluaciones de la exposición. En general, los métodos incluyen técnicas indirectas y directas, que comprenden la medición de las concentraciones en el medio ambiente y las exposiciones personales, así como biomarcadores. También se utilizan con frecuencia cuestionarios y modelos. La evaluación de la exposición requiere la determinación de las emisiones, las rutas y las velocidades de desplazamiento de una sustancia y su transformación o degradación, a fin de estimar las concentraciones a las cuales pueden estar expuestas poblaciones humanas o las distintas esferas del medio ambiente (agua, suelo y aire).

En función de la finalidad de una evaluación de la exposición, el resultado numérico puede ser una estimación de la intensidad, la velocidad, la duración o la frecuencia de la exposición o la dosis por contacto (cantidad resultante que realmente cruza la frontera). Para la evaluación del riesgo basada en la relación dosis–respuesta, el resultado normalmente incluye una estimación de la dosis. Es importante señalar que es la dosis interna, no el nivel exposición externa, la que determina el resultado toxicológico de una exposición determinada.

La caracterización del riesgo es la última etapa de la evaluación del riesgo. Está concebida para prestar asistencia a los especialistas en gestión del riesgo mediante el suministro, en lenguaje sencillo, de pruebas científicas esenciales y de los fundamentos en relación con el riesgo que necesitan para adoptar una decisión. En la caracterización del riesgo se proporcionan estimaciones del riesgo para la salud humana en los modelos de exposición pertinentes. Así pues, una caracterización del riesgo es una evaluación e integración de las pruebas científicas disponibles utilizadas para estimar la naturaleza, la

importancia y con frecuencia la magnitud del riesgo humano y/o para el medio ambiente, incluidas las incertidumbres pendientes, que razonablemente se puede estimar que se derivan de la exposición a un agente concreto del medio ambiente en circunstancias específicas.

El término "gestión del riesgo" comprende todas las actividades precisas para adoptar una decisión sobre si un riesgo asociado requiere la eliminación o una reducción necesaria. Las estrategias/opciones de gestión del riesgo se pueden clasificar a grandes rasgos como reglamentarias, no reglamentarias, económicas, consultivas o tecnológicas, que no son excluyentes entre sí. De esta manera, los mandatos legislativos (orientación reglamentaria), los aspectos políticos, los valores económicos, el costo, la viabilidad técnica, las poblaciones con riesgo, la duración y la magnitud del riesgo, la comparación de los riesgos y las posibles repercusiones en el comercio entre los países pueden considerarse, en general, como un amplio abanico de elementos que pueden influir en la formulación final de políticas o normas. Los factores fundamentales para decisión, como el tamaño de la población, los recursos, los costos del logro de los objetivos y la calidad científica de la evaluación del riesgo y las posteriores decisiones administrativas, varían enormemente del contexto de una decisión al de otra. Se reconoce asimismo que la gestión del riesgo es un procedimiento multidisciplinario complejo que raramente aparece codificado o uniforme y con frecuencia no está estructurado, pero que puede responder a aportaciones en evolución de una amplia variedad de fuentes. Cada vez se reconoce con más frecuencia que la percepción y la comunicación del riesgo son elementos importantes que también hay que tener en cuenta para lograr una aceptación pública lo más amplia posible de las decisiones en materia de gestión del riesgo.

Los productos químicos se han convertido en una parte indispensable de la vida humana, que sostienen las actividades y el desarrollo, previenen y combaten numerosas enfermedades y aumentan la productividad agrícola. A pesar de sus ventajas, los productos químicos pueden, especialmente cuando se utilizan de manera indebida, producir efectos adversos en la salud humana y la integridad del medio ambiente. La aplicación generalizada de productos químicos en todo el mundo aumenta el potencial de los

efectos adversos. Se prevé que seguirá aumentando el crecimiento de las industrias químicas, tanto en los países en desarrollo como desarrollados. En esta situación, se reconoce que la evaluación y la gestión de los riesgos de la exposición a productos químicos son una de las prioridades más importantes a la hora de aplicar los principios del desarrollo sostenible.

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